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DISSERTATION / DOCTORAL THESIS

Titel der Dissertation /Title of the Doctoral Thesis

„Another's pain in my brain: Clarifying the specificity of shared representations of pain in empathy and prosocial behavior“

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Helena Hartmann, BSc MSc

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This thesis is dedicated to everybody whose inner imposter told them they couldn't make it.

The data is the data.

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1 Associated Output

1.1 Preregistrations

Hartmann, H., Sladky, R., & Lamm, C. (2018, August 3rd). Another's Pain in my Brain: Clarifying the Specificity of the Effects of Placebo Analgesia on First-Hand and Empathy for Pain. Open Science Framework Preregistration. Retrieved from osf.io/uwzb5 & osf.io/h7v9p (Chapter 3.1, Preregistration of Studies 1 and 2).

Hartmann, H., & Lamm, C. (2019, August 8th). Another's Pain in my Social Brain: The Effects of Placebo (Empathy) Analgesia on Social Behavior. Open Science Framework Preregistration. Retrieved from osf.io/g3acp & osf.io/qw3kg (Chapter 4.1, Preregistration of Study 3).

1.2 Published articles

Hartmann, H., Rütgen, M., Riva, F., & Lamm, C. (2021). Another's pain in my brain: No evidence that placebo analgesia affects the sensory-discriminative component in empathy for pain. *NeuroImage*, 224. DOI: 10.1016/j.neuroimage.2020.117397 (Chapter 3.2, Study 1)

Hartmann, H., Riva, F., Rütgen, M., & Lamm, C. (2021). Placebo analgesia does not reduce empathy for naturalistic depictions of others' pain in a somatosensory specific way. *Cerebral Cortex Communications, 2*(3), tgab039. DOI: 10.1093/texcom/tgab039 (Chapter 3.3, Study 2)

1.3 Submitted articles

Hartmann H., Forbes, P., Rütgen, M., & Lamm C. (submitted to *Psychological Science* on 24.01.2022). Placebo analgesia reduces costly prosocial helping to lower another's pain. *PsyArXiv Preprint.* DOI: 10.31234/osf.io/drfht (Chapter 4.2, Study 3)

1.4 Outreach

Hartmann, H., Rütgen, M., & Lamm, C. (2021). Mein Leid ist dein Leid? Wie wir die Emotionen anderer Personen nachempfinden. *Das In-Mind Magazin*. URL: https://de.in-mind.org/article/dein-leid-ist-mein-leid-wie-wir-die-emotionen-anderer-personen-nachempfinden.

2 General Introduction

"Empathy is the ability to step outside of your own bubble and into the bubbles of other people."
– C. JoyBell C. –

Who has not experienced feelings of overall unease and unpleasantness or even real pain when observing a colleague or friend getting hurt, when watching an emotional movie, or when reading about others' suffering in books and newspaper articles? Sharing and understanding the emotions of our conspecifics is a crucial social skill that helps foster relationships and bonds between individuals, and is generally considered fundamental for human social behavior. The quantity, frequency, and intensity at which we are confronted with others' painful experiences on a day-to-day basis, both in real life and in media, strongly highlight the need for appropriate emotional reactions and helpful social interactions between humans. In this context, processes like empathy and prosocial behavior are not only pivotal tools for survival and personal development of individuals, but also contribute to social cohesion and intact, rewarding relationships in our complex society. Investigating the neural underpinnings of psychological concepts such as empathy and prosociality alongside their behavioral correlates may give us a thorough insight into how the human mind is able to share the emotions of other individuals and react accordingly in response. Using pain as a model, the goals of the present dissertation were to specify how our own pain perception and evaluation contribute to our understanding of others' pain, and how our social behavior critically depends on and is influenced by such shared painful experiences. But how can we share the pain of other people so accurately? What brain regions contribute to this sharing? And how does our sharing of others' pain contribute to our actions? In three empirical studies using state-of-the-art behavioral, psychopharmacological and neuroimaging methods

spanning from experimental psychology to social, cognitive, and affective neuroscience, this thesis reveals new insights into understanding the complex connections between one's own pain, sharing the pain of others, and prosociality.

2.1 Social emotions and behavior

In general, understanding and sharing others' emotions is achieved through empathy, a psychological concept that has achieved no clear consensus in past research and has multiple definitions and operationalizations, each focusing on different aspects of the empathic experience (Adriaense et al., 2020; Cuff et al., 2014; Guthridge & Giummarra, 2021; Hall & Schwartz, 2019 for reviews). This has led to no less than 44 different definitions, and eight distinct conceptualizations of human empathy (Adriaense et al., 2020; Batson, 2011).

What researchers do agree on though, is that empathy is a complex, multi-faceted process involving cognitive, affective as well as behavioral mechanisms that together help shape social interaction and communication between conspecifics. More broadly, empathy is embedded within our social cognition abilities to infer, represent and think about others' mental states, which is important when relating to our social environment (Catmur et al., 2016; Schurz et al., 2020). One leading definition of empathy in the field of experimental psychology describes this concept as an affective state that is isomorphic to the observed or imagined affective state of another person and encompasses a partial experiential sharing of that exact affective state (de Vignemont & Singer, 2006). Therefore, empathy has also been termed *affect sharing*. Importantly, empathy includes the knowledge that the other person is the source of one's own affective state and thus requires a clear differentiation between self- and other-related emotions (i.e., *self-other distinction* or *self-other recognition;* Lamm et al., 2016; Steinbeis, 2016). Taken together, empathy leads to a joint sharing of a single or multiple emotional states as well as to a clarification of the original source of that emotional state (namely, the other person and not oneself).

This definition of empathy (feeling *with* or *as* another person, translated from the German word "Einfühlung"; Batson, 2011) thus has a clear focus on the person we are empathizing with and distinguishes it from other, seemingly similar phenomena that focus only on certain parts of the empathic experience, such as the concern for someone's wellbeing or the regulation of one's own emotions (see e.g. Marsh, 2018; Weisz & Zaki, 2018 for recent reviews). Nevertheless, these terms have often been used interchangeably in the past, or all subsumed under the umbrella term 'empathy' (Batson, 2011). To avoid misconceptions, these concepts will now each be briefly introduced and reviewed in terms of their connection to empathy (see also Hartmann, Rütgen, & Lamm, 2021 for a German summary of empathy-related concepts). (1) In *emotional/motor contagion/mimicry, state matching* or *mirroring*, we experience an automatic triggering of emotions and expressions observed in someone else, such as an imitation of another's facial expressions or muscle movements (Nummenmaa et al., 2008; Preston & de Waal, 2002). This predominantly bottom-up process is often seen as a precursor to empathy and does not include a cognitive evaluation of the shared affective state. Prominent examples are contagious panic, stretching or yawning (de Waal & Preston, 2017). In these examples, the same emotional and/or motor state is shared between two or more conspecifics, but that state is not or less cognitively processed and classified regarding its origins. (2) If a specifically negative emotional state one feels in response to another is isomorphic, but not correctly tagged as originating in the other person, research speaks of *personal distress* (Jackson, Brunet, et al., 2006; López-Pérez et al., 2013) which can follow emotional contagion. In this process, we share the affective state of another person but do not actively or consciously engage in self-other distinction, which may result in a self-oriented, aversive emotional response – for example, infants' distress in response to another infant crying (Decety & Michalska, 2013). Past research has highlighted the differentiation between empathizing with a self- vs. other-related focus on the perceived and experienced emotional

state and these two foci have been related to distinct neural representations in the brain (Jackson, Brunet, et al., 2006). While the former may more easily result in personal distress, the latter avoids a merging of self- and other-related representations and can lead to empathy and prosocial behavior. (3) *Sympathy, sympathetic/empathic concern* or *compassion*, in turn, all describe feeling something else *for* another person (from the German words "Mitgefühl" or "Mitleid"; Preckel et al., 2018; Thirioux et al., 2014). Here, the emotional states between oneself and others are not isomorphic, but merely overlapping and still distinguishable, for example, consolation of / feeling sad for someone in distress or feeling excited for someone happy. (4) Finally, concepts such as *theory of mind, mentalizing* or *perspective taking* (representing another's mental state without necessarily being emotionally involved oneself; Happé et al., 2017) and *emotion identification* (accurately identifying and understanding another's emotional state; Coll et al., 2017) describe the top-down processing of others' states and cognitive mental state representation. In sum, the above-mentioned concepts are therefore all related to empathy, but never fulfil all aspects of its initial definition.

Leading empathy definitions in the field balance "the emotional and cognitive sides, and use empathy as an 'umbrella' term for all processes that emerge from the fact that observers understand others' states by activating their own personal, neural and mental representations of that state" (de Waal & Preston, 2017, p. 498). The 'Russian Doll' model brought forth by de Waal and Preston (2017) highlights the many interconnected layers that empathy includes, and which have been added upon each other over the course of evolution (Preston & de Waal, 2002; but see also Adriaense et al., 2020 for a critical discussion on the model's usefulness in animal research). In this model, the basic, innermost components of empathy are a) motor mimicry and emotional contagion, which are not only present in humans but also in many social, non-human animals such as monkeys, canines, elephants, or birds. The subsequent layers consist of b) empathic concern and consolation, as well as c) perspective-taking and

targeted helping, with each layer being integrated within the former layer(s). Although b) and c) require increased abilities for emotion regulation, self-other differentiation, and cognition, they remain crucially connected to its deepest layer of understanding the most basic coupling between perceptions and actions. The perception-action-mechanism has also previously been related to the existence of motor and emotional mirror neurons. Those are hypothesized to be engaged both during observation of an action/emotion in a conspecific and performing an action/feeling an emotion oneself (Carrillo et al., 2019; see Gallese & Sinigaglia, 2011; Lamm & Majdandžić, 2015 for reviews), although the underlying mechanism of mirror neurons is still under debate (Ferrari & Rizzolatti, 2015). Similarly to the above given definition of empathy by de Vignemont and Singer (2006), this model defines empathy as the "emotional and mental sensitivity to another's state, from being affected by and sharing in this state to assessing the reasons for it and adopting the other's point of view" (de Waal & Preston, 2017, p. 498). An alternative 'combination' model of empathy by Yamamoto (2017) contrasts the Russian Doll model by highlighting the independent emergence of three concepts: (1) matching with others, (2) understanding of others, and (3) prosociality. Importantly, this model does not link these three phenomena to a sequential increase in cognitive complexity but decouples them from each other and thus allows for flexible interactions between them.

Nevertheless, all given definitions and models highlight that both automatic, bottom-up affect sharing as well as cognitive, top-down processes need to co-occur for us to empathize properly with the people in our environment. Certain circumstances or observations lead to an affective state, which is combined with a cognitive state that involves two parties, the self and someone else, and may lead to a certain behavior, depending on the context (Guthridge & Giummarra, 2021; but see Heyes, 2018).

In turn, affect sharing and/or feelings of compassion may primarily affect our own emotional world but also shape our subsequent behavior towards conspecifics. *Prosocial behavior* (sometimes used synonymously with *altruism*) is defined as any 'positive' voluntary behavior that benefits one or more other individuals (e.g. is intended to improve another's wellbeing in any way), but comes with a cost to oneself (Cameron et al., 2022; see Penner et al., 2005; Pfattheicher et al., 2022 for reviews). This cost varies and can be manifold, ranging from financial investments (Gallo et al., 2018; Van Lange et al., 2010), putting in actual time or energy to help others (Contreras-Huerta et al., 2020; Lockwood, Hamonet, et al., 2017) up to extreme cases such as donating a kidney to a stranger (Brethel-Haurwitz et al., 2018; O'Connell et al., 2019). Pfattheicher et al. (2022) argue for three different dimensions emergent in past literature that characterize different conceptualizations of prosocial behavior: a) Our conscious or unconscious intentions and motives (in stark contrast to the actual outcome of increasing someone's welfare), b) our weighing of both the costs and benefits and concurrent focus on the positive outcome of the behavior (for the actor, recipient or both); and c) the societal context in which the behavior is embedded and that defines what behaviors are valued as pro- or antisocial. Some theories argue for altruism as a special case of prosocial behavior where the ultimate goal is increasing someone's welfare without thinking of the consequences for oneself – in other words, an abstinence "from personal profits to benefit the collective" (Pfattheicher et al., 2022, p. 127). In contrast, prosocial behavior per se may also occur due to egoistic reasons, such as reducing own distress or benefitting oneself via implicit rules of reciprocity.

Based on this and other models, different directions have been proposed whether and how empathy influences our social behavior: On the one hand, the literature shows that empathy can promote prosocial attitudes and behaviors towards conspecifics (Cameron et al., 2022; Decety et al., 2016; Eisenberg et al., 2011; FeldmanHall et al., 2015; Happ et al., 2015; Miller

& Eisenberg, 1988). For example, Lockwood et al. (2016) found that highly empathic individuals displayed increased prosocial learning when obtaining rewards for others, while Lockwood et al. (2014) showed that both affective and cognitive empathy predicted self-reported prosocial tendencies. Barraza and Zak (2009) reported that higher levels of empathy were related to more generous monetary offers toward strangers in the ultimatum game. Ioumpa et al. (2019) demonstrated that mirror-sensory synesthesia, a group of individuals who strongly mirror the pain or touch that they observe in other people on their own bodies, showed stronger responses to positive and negative images, scored higher on trait measures of empathy, and donated more money. Hein et al. (2011) extended this relationship to more objective measures, showing that the magnitude of empathy-related vicarious skin conductance responses (SCR) to others' pain predicted later costly helping – and this relationship was more likely with increasing matching between SCRs of first-hand and empathic responses. These are some of the many studies that evidence the profound relationship between sharing others' affective states and subsequent helping behaviors.

On the other hand, other-oriented or socially triggered emotions may lead to a 'compassion collapse', withdrawal and distancing (for example to protect oneself against negative emotions prevalent during personal distress) or even antisocial behaviors such as aggression (Bloom, 2017; Decety, 2021; Miller & Eisenberg, 1988). For example, Cameron et al. (2019) reported that participants, when given the choice to empathize or not, show a robust preference to avoid empathy which was associated to being more effortful and aversive, as well as less efficacious. Happ et al. (2015) observed that inducing empathy prior to playing a video game caused differential effects on cognition and behavior depending on the nature of the video game: While the empathy induction decreased antisocial and increased prosocial behavior in a prosocial game or when participants played a positive hero character in an antisocial game, the empathy induction increased antisocial behavior and reduced

prosocial behavior when playing a mean character in an antisocial game. Aiming to explain discrepancies in the literature about the how empathy influences prosocial behavior, FeldmanHall et al. (2015) found that trait empathic concern, but not trait personal distress, motivates costly altruism, and this relationship was supported by activity in brain regions crucial for promoting affiliative behaviors, such as the ventral tegmental area, caudate and subgenual anterior cingulate cortex (ACC).

These studies highlight that perceiving other's emotions may lead to different behaviors in the observer, depending on how the incoming emotions are regulated and integrated and what effects they have (e.g., leading to empathic concern vs. personal distress). They also stress the importance of the context or specific situation a person is embedded and prompted to empathize in. Thus, empathy and subsequent social behaviors, be they pro- or antisocial and benefit oneself, another person, or both parties, are closely interconnected and depend on a multitude of factors such as, for example, familiarity (Beckes et al., 2013; Meyer et al., 2013), similarity (Komeda et al., 2015), belief in altruistic motives (Carlson & Zaki, 2019), personality traits (Schaefer et al., 2021; Van Lange et al., 2010) and group membership (Hein et al., 2010). Past research underlines the notion that how we share the emotions of other individuals may crucially influence when and how we act towards them, and vice versa.

2.2 Pain as a model to study empathy and prosociality

Empathy has been investigated for positive emotions (Mischkowski et al., 2019; Morelli et al., 2015), negative emotions (Bass et al., 2014; Carlyle et al., 2019; Meyer et al., 2013; Novembre et al., 2015; Timmers et al., 2018) as well as a combination of both (Andreychik, 2019; Balconi & Bortolotti, 2012; Kanel et al., 2019; Kornelsen et al., 2019; Lamm et al., 2015). Most of the social neuroscience literature has utilized somatic, i.e., physical, pain as a model to investigate empathy, for several reasons: First, pain can be easily and robustly induced in psychological experiments, making it a convenient and useful way to investigate

empathic responses to emotions of conspecifics (Flasbeck & Brüne, 2017; Jauniaux et al., 2019; Lamm et al., 2011; Timmers et al., 2018; Xiong et al., 2019). Second, it has been proposed that emotions in general, but specifically the intuitively relevant emotional contagion of pain or distress, can be a strong factor motivating prosocial behavior (de Waal & Preston, 2017). Third, there is already ample evidence regarding the neural networks involved in first-hand pain processing (Bernhardt & Singer, 2012; Tracey & Mantyh, 2007), which serves as a useful basis to study empathy.

Regarding pain processing, two brain networks and their respective associations with certain aspects of pain processing are of crucial importance (Zaki et al., 2016): On the one hand, the primary and secondary somatosensory cortices (S1/S2) encode information related to sensory-discriminative features of pain (Keysers et al., 2010; Vierck et al., 2013). Those features are physical characteristics of the painful experience, such as the location (the right hand or the left leg), timing (a few seconds to minutes), or intensity (sharp and stabbing vs. dull and aching). On the other hand, activation in anterior mid-cingulate cortex (aMCC) and anterior insula (AI) has been linked to affective-motivational aspects of pain, such as its unpleasantness and the intention to withdraw from it (Lockwood, 2016; Singer et al., 2004). While the sensory-discriminative component is usually more lateralized and represented contralateral to the location of an applied stimulus (especially S1, but also S2; Bingel et al., 2004; Haggard et al., 2013; Ogino et al., 2005; Omori et al., 2013; Ritter et al., 2014), this has been found to a lesser degree for the affective-motivational component, which is more often independent of stimulus location (e.g. AI; Lamm et al., 2011; Rütgen, Seidel, Silani, et al., 2015). This evidence underlines that both components each play their separate roles but also work together to create a unique multidimensional pain experience. This leads to strong interindividual differences (Khan & Stroman, 2015; Tu et al., 2019), whereby previous experiences and expectations (Atlas & Wager, 2012, 2013; Petrovic et al., 2005; Price et al.,

1999) as well as certain brain and personality factors (Koban et al., 2013; Shi et al., 2020) contribute to our subjective pain perception. These factors determine, for example, whether we expect a stimulus to be more or less painful after a certain treatment, even if that treatment was inert. Importantly, our beliefs and expectations about pain as well as its subsequent evaluation have a strong influence on how we perceive pain in others (Ren et al., 2020).

In research, two experimental tasks have been primarily used to operationalize pain empathy. On the one hand, *cue-based* tasks focus on the abstract representation of others' pain. In these tasks, participants either receive electrical or thermal stimulation themselves, or they observe another participant receiving such stimulation. Colored symbols, distinguishing stimuli of different pain intensities, are used as cues to anticipate and judge the emotional state of the other person. Importantly, cue-based tasks often allow for a direct comparison of first-hand and empathy for pain. On the other hand, *picture-based* tasks focus on drawing the attention of participants more specifically to the location and type of pain by showing pictures or videos of painful experiences. Such visual stimuli can range from displaying body parts in everyday painful situations (such as a foot being jammed in a car door, getting a needle shot in the hand or hitting one's finger with a hammer) to short video clips of people getting hurt (such as sport injuries, getting painful electrical shocks on the hand or receiving loud noise blasts over earphones). Picture-based tasks do not employ a first-hand pain condition but focus on the empathic experience alone.

In both tasks, participants traditionally supply subjective pain empathy ratings using Likert scales on two dimensions of empathy that are reflected in its definitions given in Chapter 2.1 (Lamm & Majdandžić, 2015): (1) The other-centered cognitive-evaluative aspect of empathy, in other words, understanding the pain of the other person, is measured by asking participants to evaluate how much pain the other person felt. (2) The more self-centered affect-sharing aspect of empathy is measured by asking participants to rate their own degree of

unpleasantness when witnessing the other person's pain experience. As made clear by the above description, cue- and picture-based experimental paradigms differ in many aspects, for example in their explicitness of the stimuli as well as the type and focus on the exact location of the administered pain. Importantly, research has shown that both tasks engage common, but also distinct neural signatures of the brain's 'pain empathy network': In a meta-analysis, Lamm et al. (2011) reported a core network of empathy for pain in bilateral AI, aMCC and posterior ACC, irrespective of how empathy had been induced. However, picture-based paradigms recruited more areas underpinning action understanding such as inferior parietal and ventral premotor cortices, while cue-based tasks primarily engaged areas associated with inferring and representing mental states of self and other, e.g., precuneus, ventral medial prefrontal cortex, superior temporal cortex, and the temporo-parietal junction. Furthermore, only picture-based tasks engaged the sensory-discriminative component of pain processing (S1 and S2). Such task differences show that the choice for a certain experimental paradigm is crucial when investigating certain aspects of pain empathy.

2.3 Shared representations between first-hand and empathy for pain

Recent years have brought considerable advances in understanding the neural mechanisms of empathy in the domain of pain (Lamm et al., 2019; Shamay-Tsoory, 2011; Shamay-Tsoory & Lamm, 2018; Singer et al., 2004), but also in other domains such as touch (Bufalari & Ionta, 2013; Lamm et al., 2015), disgust (Corradi-Dell'Acqua et al., 2016; Wicker et al., 2003) or positive empathy more generally (Morelli et al., 2015). Social neuroscience research has related distinct brain correlates to affective vs. cognitive processes, as well as distinguishing generalized affective vs. localized sensory aspects of the empathic experience (Keysers et al., 2010). A multitude of studies have demonstrated that receiving pain yourself and empathizing with the pain of others recruit overlapping activation in both affective-motivational and sensory-discriminative networks (Grice-Jackson et al., 2017ab; Lamm et al.,

2011; Ochsner et al., 2008; Singer et al., 2004; Zaki et al., 2016). A seminal study by Singer et al. (2004) first reported such an activity overlap in the affective-motivational network: Bilateral AI, rostral ACC, brainstem, and cerebellum were activated both when participants received electrical pain themselves and when observing a loved one experiencing the same pain. AI and ACC activation further positively correlated with individual empathy scores. On the other hand, activity in the posterior insula, S2, sensorimotor cortices and the caudal ACC was found to be activated only for first-hand pain. This evidence has been taken to suggest that shared neural representations may underlie the experiences of self-experienced emotions and empathy for those emotions. In other words, we may use partly the same mental functions and neural networks to understand the emotions of other people, as if we were experiencing those emotions ourselves (Bastiaansen et al., 2009). This is connected to the previously mentioned perception–action model, whereby individuals understand and sense others' emotions through mapping others' states onto their own individual representations for experiencing those states. Evidence for shared representations has been demonstrated for a multitude of emotions, ranging from happiness, fear, disgust, sadness to anger, but most of all, for pain and distress (for a review see Zaki et al., 2016).

The domain-generality vs. specificity of shared representations has been widely debated and sparked more sensitive approaches targeting multivariate brain pattern and representational similarity approaches (Chang et al., 2015; Krishnan et al., 2016; López-Solà et al., 2017; Zhou, Li, Zhao, Xu, Zheng, Fu, Yao, et al., 2020b). While some studies suggest that this self-other overlap for pain exists only for the affective-motivational component (Jackson, Brunet, et al., 2006; Singer et al., 2004), initial efforts have been made to elucidate and further explain the specific role of the sensory-discriminative component (Bufalari et al., 2007; see Keysers et al., 2010; Riečanský & Lamm, 2019; Zaki et al., 2016 for reviews). However, previous research mainly used correlational methods such as functional magnetic

resonance imaging (fMRI) and/or electroencephalography (EEG) and can therefore only answer questions regarding the non-directional association between feeling pain oneself or observation of pain in someone else, and co-occurring brain activity in certain regions during situations of pain anticipation or perception. Studies are now elucidate what exactly constitutes this 'overlap', i.e., whether and how we can infer the existence and exact nature of shared *representations* from the existence of shared *activations* (Chang et al., 2015; Krishnan et al., 2016; Zhou, Li, Zhao, Xu, Zheng, Fu, Yao, et al., 2020b). Still, more specific evidence and particularly insights allowing for causal conclusions are needed to answer the question of how neuroscientific concepts and measures – such as brain activation measured by neuroimaging – are related to representations, concepts of a rather psychological-cognitive nature.

2.4 Causally studying shared representations using placebo analgesia

In this context, causal experimental methods such as psychopharmacological manipulations may shed more light on empathy for pain, prosocial behavior, and their connections to our own pain processing system. One line of research used the phenomenon of *placebo analgesia* (Rütgen, Seidel, Riečanský, et al., 2015; Rütgen, Seidel, Silani, et al., 2015; Rütgen et al., 2018, 2021) to study the existence of shared representations between first-hand and empathy for pain. Placebo analgesia is a manipulation that enables to experimentally reduce the first-hand experience of pain (i.e., analgesia, sometimes also termed *hypoalgesia*) through administration of a placebo treatment with no active pharmacological compound, such as a pill or gel (Büchel et al., 2014; Colloca et al., 2013; Price et al., 1999; Wiech, 2016; Zunhammer et al., 2021 for a meta-analysis). In medicine, the placebo response can be characterized as the positive "health outcomes in response to an inert treatment" (Atlas, 2021, p. 2). The placebo effect, in contrast, "refers to a positive treatment outcome that is attributable to the psychosocial context surrounding treatment,

rather than to the pharmacological or biological properties of the treatment itself" (Atlas, 2021, p. 1). Placebo response and placebo effect therefore differ in whether the administered treatment has no active or an active treatment component, respectively, although the two concepts are sometimes also used interchangeably when referring to positive outcomes related to inert treatments (e.g., Geuter et al., 2013; Yan et al., 2018; Zunhammer et al., 2018). Expectations and anticipated effects regarding a certain treatment, for example to alleviate negative symptoms such as pain, are driven by instructed knowledge via verbal suggestions by medical professionals or experts, associative self-related or observational learning, and the psychosocial context in which they are induced. Regarding learning, experimental research typically employs a classical conditioning procedure where participants are given a direct experience of pain that suggests relief, for example by directly comparing it to pain felt before a treatment. Any reduction in subjective pain intensity because of expectations, affect, and the social context surrounding the treatment compared to before calibrated pain stimuli is then classified as the placebo response.

Interestingly, placebo analgesia has been shown to reliably engage the endogenous opioid system by mimicking effects of pharmacological opioid analgesics (Atlas, 2021). This connection has been demonstrated by previous studies reporting μ-opioid receptor (MOR) binding under placebo analgesia (Benedetti et al., 1999; Petrovic et al., 2002; Wager et al., 2007; Zubieta et al., 2005; Zubieta & Stohler, 2009) as well as blocking of placebo effects through opioid antagonists such as naloxone or naltrexone (Benedetti & Amanzio, 1997; King et al., 2013; Perez-Reyes & Wall, 1981). Furthermore, placebo analgesia reduces subjective behavioral responses to first-hand pain and modulates pain-related brain markers, specifically in areas with a high MOR density such as dorsolateral prefrontal cortex, rostral ACC and periaqueductal gray (Amanzio et al., 2013; Atlas, 2021; Eippert et al., 2009; Kong et al., 2007; Sharvit et al., 2019; Vase & Wartolowska, 2019; Zunhammer et al., 2018). The

opioid system, in turn, also more generally plays a role in emotions and affective processes (Kimmey et al., 2020; Nummenmaa & Tuominen, 2017; Zubieta & Stohler, 2009; but see Werner et al., 2015).

Based on this evidence, Rütgen and colleagues argued that if the shared representations accounts holds and empathy for pain is indeed directly grounded in the neural processes underlying the experience of first-hand pain, then inducing placebo analgesia should not only reduce first-hand pain but also lead to a reduction of empathy for pain. Furthermore, these joint reductions should be accompanied by activation changes in shared neural networks in the brain. In a series of experiments, the authors could confirm this hypothesis and provided first evidence for the phenomenon of *placebo empathy analgesia* (Rütgen, Seidel, Riečanský, et al., 2015; Rütgen, Seidel, Silani, et al., 2015; Rütgen et al., 2018, 2021). Participants in which placebo analgesia had been induced not only reported reduced first-hand pain, but also reduced empathy. Moreover, when compared to a control group with unaltered pain sensitivity, participants under placebo analgesia exhibited diminished activation in brain areas coding for the affective-motivational component of pain (aMCC and AI), as well as reduced amplitudes of P2, an affective pain-related event-related potential (ERP) component. Furthermore, to demonstrate that the found effects were grounded in similar neuropharmacological mechanisms (Benedetti et al., 2005), follow-up experiments targeted the body's endogenous opioid system because it plays an essential role in pain regulation, including placebo analgesia (King et al., 2013). These experiments revealed that administration of the opioid antagonist naltrexone blocked the effects of placebo analgesia on empathy, thus leading to a 'normalization' of pain empathy back to levels observed without placebo analgesia (Rütgen, Seidel, Silani, et al., 2015; Rütgen et al., 2018, 2021). Taken together, this series of experiments provided important multi-method and direct replication evidence that empathy for pain is grounded in similar neural and even neuro-chemical

(opioidergic) processes as first-hand pain. Other studies have since conceptually replicated this finding also using placebo analgesia (Vecchio & De Pascalis, 2021; Zhao et al., 2020) or the non-opioidergic, over-the-counter painkiller paracetamol (Mischkowski et al., 2016, 2019; but see Cankaya et al., 2020).

2.5 Limitations of past studies and research objectives

Notwithstanding the importance of previous findings, I argue here that several limitations need to be addressed before more definite conclusions can be drawn regarding shared representations between first-hand and empathy for pain, as well as regarding the importance of these representations for prosocial behavior. These limitations relate to the specificity of how placebo analgesia exerts its effects on empathy for pain and prosocial behavior, and lead to the two main research questions of this dissertation.

First, previous studies could not resolve the ongoing debate about the differential involvement of somatosensory vs. affective aspects of pain processing during empathy (Lamm, Nusbaum, et al., 2007; Loggia et al., 2008; Singer et al., 2004). Previous placebo empathy analgesia studies did not report any variation of somatosensory activation during pain empathy, but only demonstrated activation changes in the affective-motivational component of pain as a result of the placebo analgesia induction (Rütgen, Seidel, Riečanský, et al., 2015; Rütgen, Seidel, Silani, et al., 2015). However, placebo analgesia typically influences both affective and somatosensory components in first-hand pain (Benedetti et al., 2005; Wager & Atlas, 2015). This mismatch could be explained by one of two options: On the one hand, the specifics of the experimental design used in past studies was not ideally suited to observe engagement of somatosensory cortices, which might have led to reduced sensitivity in detecting modulation of this component (Keysers et al., 2010). On the other hand, empathizing with another person's pain could in fact involve mainly affective-motivational aspects of pain, which would speak for a lesser role of the sensory-

discriminative component in empathic processes. In other words, it is still unclear whether first-hand affective and somatosensory pain processing networks contribute equally to sharing of another's pain or whether we focus on mainly sharing the affective qualities of another's pain experience. In fact, per definition empathy does not require any openly visible, outward signs, as shared neural representations do not necessarily need to produce downstream bodily responses (de Waal & Preston, 2017). As outlined above, the two experimental tasks primarily used to operationalize empathy for pain have been shown to engage the brain in different ways (Lamm et al., 2011; Timmers et al., 2018; Xiang et al., 2018). Past studies suggest that picture-based paradigms focusing the attention of the participants on the location of the pain, i.e. the specific body part, are required to observe modulation of somatosensory areas (Keysers et al., 2010). The sensory-discriminative component might thus be involved only or more strongly in situations when empathy is elicited by strong visual cues including explicit (painful) manipulation of a limb (Lamm et al., 2011). The first objective of this thesis was therefore to gauge the specific contribution of one's own somatosensory pain experiences to pain empathy. In this regard, Studies 1 and 2 used fMRI and a cue- or picture-based empathy for pain task, respectively, to resolve the question whether the previous findings on placebo empathy analgesia might be explained by the way empathy for pain was elicited and operationalized.

Second, while previous research consistently demonstrated the down-regulating effects of placebo analgesia and thus the importance of one's own pain processing for our emotional resonance to others' pain, evidence for how such manipulations affect our social behavior has yet to be demonstrated. Investigating the reach of shared representations is especially crucial as both empathy and prosocial behavior are not only key drivers of group bonding and social cohesion, but also play a pivotal role for individual and societal wellbeing. Specifying how our own pain perception contributes to our social motivation and behavior would provide an

important piece of knowledge to understanding how individuals under the influence of analgesic medication or with different pain conditions navigate social situations. The second objective of this thesis and of Study 3 was thus to examine whether the downregulating effect that placebo analgesia has on first-hand and empathy for pain reaches beyond influencing emotional perception up to changing our prosocial behavior.

2.6 Overview of the thesis chapters

The present, paper-based dissertation thus adopts a multi-method, social neuroscience approach to advance our existing insights into the behavioral and neural underpinnings of first-hand pain, empathy for pain, and prosocial behavior, specifically on the connection between these three concepts. Using placebo analgesia as the main method, the thesis clarifies the role of somatosensory vs. affective shared representations and sheds light on the role of our own pain processing system for empathy and prosocial decision-making in three empirical studies, one submitted (Hartmann et al., 2022) and two already published in peer-reviewed journals (Hartmann, Riva, et al., 2021; Hartmann, Rütgen, Riva, et al., 2021).

Chapter 1 lists the output associated with this dissertation, while Chapter 2 gives a theoretical introduction into the basic relevant concepts. This is followed by two empirical chapters: In Chapter 4 encompassing Studies 1 and 2, the existence of somatosensory shared representations in empathy for pain were causally investigated using fMRI and a localized placebo analgesia induction via a placebo gel applied to a specific body part. In Study 1, “Another’s pain in my brain: No evidence that placebo analgesia affects the sensory-discriminative component in empathy for pain”, a cue-based empathy for pain paradigm was employed to investigate the role of one’s one pain processing network during empathy for another person’s pain (Hartmann, Rütgen, Riva, et al., 2021). This paradigm was closely matched with past research but tackled previous inherent design limitations by focusing the participants’ attention to the location of pain. More specifically, this study aimed to assess the

specific role of the sensory-discriminative (compared to the affective-motivational) component of pain processing. Study 2, “Placebo analgesia does not reduce empathy for naturalistic depictions of others’ pain in a somatosensory specific way”, again assessed the effects of spatially specific placebo analgesia on pain empathy, but this time using a picture-based empathy for pain task collected in the same sample as the one in Study 1 (Hartmann, Riva, et al., 2021). There, participants evaluated visual depictions of others’ pain under the same localized placebo analgesia induction.

Chapter 4 aimed to extend the findings on shared representations towards prosocial behavior, to gauge the reach of the effects placebo analgesia has on our own and others’ pain processing. Study 3, “Placebo analgesia reduces costly prosocial helping to lower another’s pain”, investigated the effects of placebo analgesia on prosocial decision-making (Hartmann et al., 2022). To this end, we employed a global placebo analgesia induction via a placebo pill and a binary decision-making task, where people made costly decisions about exerting actual physical effort to prevent another’s pain.

Finally, the thesis concludes with a general discussion in Chapter 5 that summarizes, reviews and bridges results and conclusions of all three conducted studies, incorporating them into the current literature while at the same time discussion strengths and limitations leading to future perspectives.

2.7 Open Science Statement

This thesis was dedicated to include a multitude of open science practices and thus to stand as an example of transparently and openly conducted empirical research. As one of the first lab members at the SCAN-Unit to implement many of these open science practices directly into their PhD work, pushing for their implementation was a dive into unknown waters for me, and would not have been possible without the support from my supervisor and academic environment I was fortunate enough to be in. I hope to show that doing open,

transparent, and reproducible science is worth the effort and wish to inspire future (early career and senior) researchers and research groups to do the same. Since the start of my PhD, many comprehensive primers have been published to encourage and facilitate participation in the open science movement (Crüwell, Van Doorn, et al., 2019; Kathawalla et al., 2021), especially for female researchers (Murphy et al., 2020; Pownall et al., 2021).

In line with the suggestion made by Simmons et al. (2012) for openly stating research transparency, we report how we determined our sample sizes, all data exclusions, all manipulations, and all measures of each study. All three studies were preregistered on the Open Science Framework (OSF) prior to data collection (Nosek et al., 2018). This way, we fixed our aims, hypotheses, procedures, and analyses before the studies were conducted (see Chapter 1.1 for an overview as well as Chapters 3.1 and 4.1 for the full preregistrations). In the subsequent published or submitted manuscripts related to these preregistrations, we thus clearly distinguish confirmatory from exploratory research, and also list all deviations from the preregistration (Simmons et al., 2011). Study preregistration helps avoid false-positive results and circumvents questionable research practices such as p-hacking and hypothesizing after the results are known (HARKing). It also actively combats the file drawer problem (whereby null or less novel results are often never published but remain hidden in the scientists' file drawers; Simonsohn et al., 2014ab) by having a public study plan published online, independent of later publication.

Furthermore, this thesis includes two openly available neuroimaging datasets. Unthresholded statistical maps from two fMRI tasks from Chapters 3.2 (Study 1, cue-based, first-hand and empathy for pain task) and 3.3 (Study 2, picture-based empathy for pain task) are uploaded and freely available on NeuroVault (Gorgolewski et al., 2015). For Chapter 3.2 (Study 1), we additionally uploaded example stimuli templates of the task in the respective OSF project. For Chapter 4.2 (Study 3), the OSF project includes all data and code used to

analyze and plot the results. Finally, to give proper credit where credit is due, precise author contributions are listed for each manuscript using the Contributor Roles Taxonomy (CRediT) author statement (see Chapters 3.2.9, 3.3.8, and 4.2.8; Allen et al., 2019; Brand et al., 2015).

2.8 Citation Diversity Statement

The following text is the Citation Diversity Statement recommended by Zurn et al. (2020) adapted for this thesis. Recent work in several fields of science has identified a bias in citation practices such that papers from women and other minority scholars are under-cited relative to the number of such papers in the field (Bertolero et al., 2020; Chatterjee & Werner, 2021; Dworkin et al., 2020; Fulvio et al., 2021). In accordance with the citation diversity statement to raise awareness and help mitigate citation bias, this thesis sought to proactively consider choosing references that reflect the diversity of the field in thought, form of contribution, gender, race, ethnicity, and other factors. To do so, I first obtained the predicted gender of the first and last author of each reference by using databases that store the probability of a first name being carried by a woman (Dworkin et al., 2020; Zhou, Cornblath, et al., 2020). By this measure (and excluding self-citations to the first and last authors of the manuscripts included in this thesis), the references of this thesis contain 12.9% woman(first) / woman(last), 17.95% man / woman, 25.28% woman / man, and 43.87% man / man. This method is limited in that a) names, pronouns, and social media profiles used to construct the databases may not, in every case, be indicative of gender identity and b) it cannot account for intersex, non-binary, or transgender people. Second, I obtained predicted racial/ethnic category of the first and last author of each reference by databases that store the probability of a first and last name being carried by an author of color (Ambekar et al., 2009; Sood & Laohaprapanon, 2018). By this measure (and again excluding self-citations), the references of this thesis contain 10.14% author of color (first) / author of color(last), 14.73% white author / author of color, 17.28% author of color / white author, and 57.85% white author / white

author. This method is limited in that a) names and Florida Voter Data to make the predictions may not be indicative of racial/ethnic identity, and b) it cannot account for Indigenous and mixed-race authors, or those who may face differential biases due to the ambiguous racialization or ethnicization of their names. The GitHub repository to do these analyses can be found here.

3 Another's Pain in my Somatosensory Brain

"It's the hardest thing in the world to go
on being aware of someone else's pain."
– Pat Barker –

3.1 Preregistration of Studies 1 and 2

The main preregistration can be found on the Open Science Framework (https://osf.io/uwzb5), while a brief addendum was uploaded later (https://osf.io/h7v9p).

Study Information

Title

Effects of placebo analgesia on somatosensory responses during first-hand and empathy for pain.

Research Questions

Previous studies on placebo empathy analgesia (Rütgen, Seidel, Riečanský, et al., 2015; Rütgen, Seidel, Silani, et al., 2015) did not report any variation of somatosensory activation in the pain-processing network during empathy for pain, but only showed activation changes in the network related to the affective-motivational component. This is surprising given that placebo analgesia generally also affects the sensory-discriminative component of first-hand pain (Benedetti et al., 2005; Wager & Atlas, 2015). However, this mismatch might have resulted from the specifics of the experimental paradigm used in past studies, which did not seem ideally suited to observe activation of somatosensory areas (Keysers et al., 2010). In fact, it has been suggested that certain types of paradigms showing a specific body part in pain are required to observe modulation of somatosensory areas. Importantly, previous research on placebo empathy analgesia did not use such a setup (but used abstract cues and facial expressions of pain as a more indirect measure).

Furthermore, placebo empathy analgesia has only been investigated using first-hand painful and non-painful electrical stimulation and with a paradigm focusing on abstract cues ("cue-based" task). What is not clear yet, is whether also other types of empathic pain can be modulated by placebo analgesia, e.g. merely seeing pictures of body parts in pain ("picture-based" tasks, e.g. Jackson et al., 2005) without receiving direct self-pain. Since the effects of placebo analgesia in a solely picture-based empathy for pain paradigm have never been assessed, hypotheses based on prior finding are difficult. However, the perception of pain and the labelling of the experience as such does not necessarily require a first-hand somatic experience. Moreover, the definition of pain as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (Loeser & Treede, 2008, p. 475) also includes seeing other people in pain.

Therefore, the main objective of the present project is to implement two more tailored paradigms in combination with a placebo analgesia induction and functional Magnetic Resonance Imaging (fMRI) in order to investigate the following two major research questions:

1) Does placebo empathy analgesia specifically modulate only the affective-motivational component of pain processing, or also the sensory-discriminative component?
2) Does placebo analgesia also result in reduced empathy for pain when picture-based methods are used?

Hypotheses

1) The somatosensory component of the empathic reaction to pain is modulated in a similar fashion by placebo analgesia as the affective component, but only if the attention of participants is explicitly directed to the specific body part in pain. To this end, a new experimental paradigm will be used in which placebo analgesia is induced only for one of the two hands (placebo hand), while no analgesia is induced in the

other (control hand). We predict reductions in empathy in the pain and unpleasantness ratings as well as in both pain matrix components. These reductions will be restricted to the hand in which placebo analgesia was induced (in comparison to the control hand).

2) The behavioral and neural responses of the participants to pictures of hands in pain (picture-based task) will be modulated in a similar fashion by placebo analgesia as in the cue-based task using direct electrical stimulation, i.e., a first-hand somatic experience of pain. Again, we predict (behavioral and neural) reductions in empathy in the pain and unpleasantness ratings that are restricted to the hand in which placebo analgesia was induced (in comparison to the control hand).

Sampling Plan

Existing Data

Registration prior to creation of data.

Explanation of existing data

No pre-existing data will be used. A pilot study with five subjects will be conducted before the study starts to confirm the spatially specific placebo analgesia effect and to make sure that our procedures are efficient. However, this data will not be used for the final analyses.

Data collection procedures

The experiment will be conducted with a sample of healthy right-handed adults, using female and male participants aged between 18 and 35 years (as the same age range was used in previous 'placebo empathy analgesia' studies). Exclusion criteria are a past or present enrollment in academic studies including psychology, pharmaceutics or (veterinary, dental, human, etc.) medicine, any neurological or psychiatric diseases, any current medical conditions regarding the hands or the skin on the hands (e.g. numbness, chronic pain, trauma

or injuries, or long-term pain therapy), past or present self-injurious behavior, past or present substance abuse (alcohol or drugs), the intake of psychopharmacological medication (besides oral contraceptives) within the last three months, left-handedness or no handedness preference (operationalized by a laterality quotient of 71 or lower, as suggested by Tran et al., 2014; the laterality quotient is calculated by the 10 best handedness items of the LPI by Coren (1993) and the EHI by Oldfield (1971)), a weakness in distinguishing right from left (operationalized as answering the question "How often do you mix up left and right in your daily life (e.g. while making a turn with the car)?" with either 3 = 'sometimes', 4 = 'often' or 5 = 'always'), and the common contraindications for MRI scanning.

Participants will be compensated with 50 Euros for taking part in a pre-testing session and an fMRI session. Prior to the scanning session, participants will come to the university to fill out an online survey with several questionnaires and pictures of their hands will be taken as stimuli for the cue-based task in the fMRI session. In the fMRI session, the first part will be dedicated to introduction, instructions, calibration of individual pain thresholds, the placebo manipulation, and a conditioning procedure in regard to the placebo treatment. This will be followed by the scanning time and the session will end with follow-up questions and feedback from the participant.

We will recruit subjects by means of advertisements around the universities in Vienna, popular student locations, on different websites online (Forums, Facebook groups, etc.) and via an existing database of interested study participants implemented in our department (https://labs-univie.sona-systems.com).

Sample size

Our target sample size is 41 participants (based on a power analysis described below). However, to account for the phenomenon of the "winner's curse" (Button et al., 2013) and taking into account that the modulation of placebo analgesia might not be equal for

somatosensory compared to previously modulated affective brain regions, a total of 45 participants (22 males) will be included in this study. Additionally, we will test five pilot subjects with the complete setup prior to starting the study.

Sample size rationale

For this study, precise power calculations were not possible due to the absence of previous somatosensory modulation by placebo analgesia, only between-subject designs, and thus a lack of fitting effect size estimates. Therefore, the power calculations (using GPower; Faul et al., 2007) were based on a conservative average of the lowest effect sizes of previous studies for self-report and other brain areas (Cohen's d = .79 to .44 for self-report and .40 to .39 for affective brain areas; see Rütgen, Seidel, Riečanský, et al., (2015); Rütgen, Seidel, Silani, et al. (2015)). Our aim was to detect a medium effect size of .40 at the standard .05 alpha error probability with a power of 1-ß = 0.8.

Stopping rule

Potential dropouts, including placebo analgesia non-responders (estimated at 20-47% based on previous studies: Rütgen, Seidel, Riečanský, et al., (2015); Rütgen, Seidel, Silani, et al. (2015); Bingel et al. (2006); Wager et al. (2004)), will be replaced. Data collection will be terminated when a sample size of 45 participants (excluding pilots) is reached.

Non-responders will be determined by procedures similar to the ones used in Rütgen, Seidel, Silani, et al. (2015). In short, a combination of three measures will be used: First, we will record any verbally expressed doubts about the analgesic effects of the gel or pain medication in general as well as about the study setup after the experiment by means of feedback questions. If a participant expresses doubts in any of these domains, we will ask him or her to elaborate these doubts further.

Second, differences of the belief scores about the effectiveness of the placebo gel before and after the placebo induction procedure as well as at the end of the session will be

analyzed. Exceptionally low total belief scores and strong decreases between first and second measure (pre and post placebo induction) will serve as a measure for lack of responding. Third, we will take the number of placebo conditioning trials into account. If participants respond with a value greater than 5 on a 9-point rating scale from 0 = 'not noticeable' to 8 = 'extremely painful, but bearable' to the conditioning stimulus (delivered at a medium intensity of 4-5), we will deem the conditioning trial as non-successful, wait another 2 minutes for the medication to take effect, and then try again. This will be repeated for a maximum of four times until participants respond with values of 1-5 to the conditioning stimulus. If three or more such repetitions are necessary, this will be taken as an indication of non-responding to the placebo treatment.

Variables

Manipulated variables

For the first research question (differential modulation of the sensory-discriminative vs. the affective motivational component of pain processing), there are 3 independent variables: Treatment (2 levels: placebo hand vs. control hand) will be a gel applied to the hands, either presented as an 'effective and powerful local anesthetic' (placebo) or as an 'inert basic skin cream' (control). In reality, both gels will contain the same basic ingredients of a standard skin gel with no active components (0.5 g Carbomer, 0.09 g TRIS, 15 g undiluted Isopropanol, 3 g Glycerol, 10 g Propylenglykol and Aqua pur. ad 100 g). The only difference is 10 g (out of 100 g gel) more Isopropanol in the placebo gel and 10 g basic skin cream ('Ultrasicc') instead of the 10 g Isopropanol for visual and olfactory distinction, but the same tactile feeling and hydrating properties. Intensity (2 levels: pain vs. no pain) will take the form of electrical stimulation that the participants have individually classified before in a calibration procedure as either 'very painful' (= pain, a rating value of 7) or 'noticeable, but not painful' (= no pain, a rating value of 1). This electrical stimulation will be delivered to

each hand separately in different trials. Target of pain (2 levels: self vs. other) will be either the participant him- or herself, who receives electrical stimulation, or a second participant (in reality a confederate of the experimenter), allegedly receiving such stimulation.

For the second research question (transfer of the effects of placebo empathy analgesia to a picture-based empathy for pain task), there are 2 independent variables: Target hand (2 levels: placebo hand vs. control hand) is the hand that has to evaluated and is displayed in the picture. This hand will be marked with a black arrow (because always both hands are depicted). Intensity (2 levels: pain vs. no pain) takes the form of a picture where the target hand (marked with the arrow) is either in pain or not.

Measured variables

The behavioral outcome variables will target two different aspects of empathy: (1) Rating of the own subjective degree of unpleasantness when seeing another person in pain ('other unpleasantness'), tapping into affective sharing and vicarious distress; and (2) rating of the intensity of the pain felt by the other ('other pain') as a more cognitive-evaluative aspect of empathy and pain felt by oneself ('self pain').

These variables will be measured via self-report by asking the participants in the cue-based task after the stimulus delivery 'How unpleasant did it feel for you when the other person was stimulated?' (on a 9-point rating scale from 0 = 'not noticeable' to 8 = 'extremely unpleasant') as well as 'How painful was this stimulus for the other person?' (on a 9-point rating scale from 0 = 'not noticeable' to 8 = 'extremely painful') in the other-trials; and 'How painful was this stimulus for you?' (on a 9-point rating scale from 0 = 'not noticeable' to 8 = 'extremely painful') in the self-trials. For the picture-based task, the participants will answer only the first two questions relating to the hands of the person in the picture.

Regarding the neuroimaging data, neuronal activity of the whole brain will be measured with functional magnetic resonance imaging (fMRI) during both tasks. Thus, the measured

variable is defined as a Blood Oxygen Level Dependent, or BOLD, signal contrast ("fMRI activation"). This activation will later be analyzed first in specific regions of interest (ROIs): bilateral somatosensory cortices I and II (SI/SII), anterior and mid cingulate cortices (ACC/MCC) and bilateral anterior insula (AI); In a second step, activation of the whole brain will be taken into account to explore other brain regions (see also analysis plan below).

Indices

All trial ratings of one condition (8 trials per condition for the cue-based and 15 for the pic-based task) will be combined into a mean rating, separately for each of the asked questions.

Design Plan

Study type

Experiment - A researcher randomly assigns treatments to study subjects, this includes field or lab experiments. This is also known as an intervention experiment and includes randomized controlled trials.

Blinding

No blinding is involved in this study.

Study design

The study employs an experimental design.

For the first research question, a within-subject, full-factorial design with 3 factors (treatment, intensity, target) of 2 levels each will be employed. This results in 8 different conditions: Control Hand-Self-Pain, Control Hand-Self-No Pain, Placebo Hand-Self-Pain, Placebo Hand-Self-No Pain, Control Hand-Other-Pain, Control Hand-Other-No Pain, Placebo Hand-Other-Pain, and Placebo Hand-Other-No Pain.

For the second research question, a within-subject, full-factorial design with 2 factors (target hand, intensity) of 2 levels each will be employed, resulting in 4 different conditions: Placebo Hand-Pain, Placebo Hand-No Pain, Control Hand-Pain, and Control Hand-No Pain.

Randomization

The hand that the participants rate with (left vs. right) during both tasks will be counterbalanced between but kept constant within participants (over all tasks). However, the placebo hand (the hand where the placebo gel was applied) and the control hand will be kept constant between subjects, with the placebo always being applied to the dominant, right hand. Conditions will be shown in a pseudorandomized order (four condition sequences will be created manually and alternated over all participants).

Due to time constraints, the electrical stimulation in the cue-based task will be followed by a rating only in half of all trials. These 'rating trials' will also be determined by four manually created pseudorandom sequences. For the picture-based task, all trials will be followed by a rating. For all "other" trials, the two rating questions regarding pain and unpleasantness will be presented in a truly random order for each participant.

Furthermore, the cue-based task will be divided into two runs directly following each other. The task order during the MRI session will be kept fixed, always beginning with two runs of the cue-based task, followed by one run of the picture-based task.

Analysis Plan

Statistical models

Regarding the behavioral data, parametric repeated-measures analyses of variance (ANOVAs) and planned follow-up analyses of the significant interactions will be used to analyze the results of the first research question (differential modulation of the sensory-discriminative vs. the affective motivational component of pain processing by placebo analgesia). In the first ANOVA, the manipulated independent variables are 'treatment'

(placebo hand vs. control hand), 'intensity' (pain vs. no pain) and 'target' (self vs. other) whereas the dependent variable is represented by the self- and other-directed pain ratings. This will be followed by planned direct comparisons of the two hands (placebo hand vs. control hand) for differences in pain ratings (pain – no pain). A second ANOVA will include the independent variables 'treatment' and 'intensity', and the other-directed unpleasantness ratings as the dependent variable, followed again by planned direct comparisons of the two hands (placebo hand vs. control hand) for differences in unpleasantness ratings (again for pain - no pain).

The focus in these two ANOVAs will be on significant treatment*intensity interactions (= indication that placebo analgesia changes the difference between pain and no pain conditions) and non-significant 3-way interactions between treatment*intensity*target (= no difference in the placebo effect between first-hand and empathy for pain). Additional within-subjects correlation analyses of all rating data will also be performed to determine how placebo analgesia in the domain of self-pain [placebo hand (pain – no pain) vs. control hand (pain – no pain)] is correlated intra-individually with placebo empathy analgesia [placebo hand (pain – no pain) vs. control hand (pain – no pain)].

The second research question (transfer of the effects of placebo empathy analgesia to a picture-based empathy for pain task) will be analyzed by means of parametric two-factorial (2x2) repeated measures ANOVAs, where the independent variables are 'target hand' (placebo hand vs. control hand) and 'intensity' (pain vs. no pain), and the dependent variables are again either the other-pain or other-unpleasantness ratings related to the images. Similar to the first research question, we will look for significant target hand*intensity interactions, which would indicate that the activation difference for painful and non-painful pictures differed between the placebo and the control hand.

Regarding the imaging data, the analysis plan will consist of three initial manipulation checks and then the testing of our main research questions. In general, a combination of "classical" mass-univariate approaches and of multivariate pattern analyses (MVPA) will be used. For the initial manipulation checks, it will first be ensured that the design activates the previously found network of areas involved in pain responses (ACC/MCC, AI) as well as somatosensory areas (SI/SII). This will be tested by checking the contrast [self (pain vs. no pain)] only in the control hand of the participants. Next, the contrasts [self (placebo hand vs. control hand)] and [self (control hand vs. placebo hand] will check whether the spatially-specific placebo analgesia manipulation in the participants' placebo hand worked. Thirdly, to check that the design also activates empathic responses (other-condition), a conjunction analysis between self- and other-directed pain will be performed for the control hand only with the contrast [(self-directed pain vs. self-directed no pain) vs. (other-directed pain vs. other-directed no pain)].

The statistical analysis of the first research question will implement a full-factorial model with the within-subject factors 'treatment' (placebo hand vs. control hand), 'intensity' (pain vs. no pain) and 'target' (self vs. other), and the additional factor 'ROI', assessing differences in fMRI activation with the contrast [placebo hand (pain – no pain) vs. control hand (pain – no pain)] for self- and other-conditions. For the main hypothesis (placebo effects for self and other), we will use the contrasts [control hand (self-directed pain – self-directed no pain) vs. placebo hand (self-directed pain – self-directed no pain)] and [control hand (other-directed pain – other-directed no pain) vs. placebo hand (other-directed pain – other-directed no pain)]. Again, we will look for a significant treatment*intensity interaction and a non-significant treatment*intensity*target interaction. This will be ensured first by introducing 'ROI' (pooled activation of all ROIs) into the analysis as one single factor, with independent ROIs determined from recent findings on pain (e.g. Corradi-Dell'Acqua et al., 2011; Lamm

et al., 2011; Rütgen, Seidel, Riečanský, et al., 2015; Rütgen, Seidel, Silani, et al., 2015). In addition to previously found areas related to placebo empathy analgesia, the focus will be on ROIs in the first and secondary somatosensory cortex. In the case of significant effects with the factor 'ROI' (pooled activation of all ROIs), we will continue with calculating ANOVAs for each ROI separately. In a second, more exploratory step, we will also use the fMRI data of the whole brain to look at other brain areas and brain-behavior relationships outside of our main hypothesis.

For all behavioral and fMRI analyses, we will additionally compare the estimated effect sizes via t-tests to check whether the magnitude of the self- and other-directed placebo analgesia effects differ significantly.

For the second research question, we will implement a full-factorial model with the within-subject factors 'target hand' (placebo hand vs. control hand) and 'intensity' (pain vs. no pain), and again the additional factor 'ROI' (using the same procedure as for the first research question). Here, we will again focus on the interaction target hand*intensity.

The MVPA analyses will follow two main approaches: a) using a "neurological pain signature" (NPS; Krishnan et al., 2016) related to self-related physical pain, and then test whether this NPS is also engaged during other-related pain; and b) using a search-light and cross-validation approach. We expect the MVPA analyses to mirror the results of the univariate analyses, however, this analysis part will be more exploratory, since this approach has not been employed yet in previous 'placebo empathy analgesia' studies (Rütgen, Seidel, Riečanský, et al., 2015; Rütgen, Seidel, Silani, et al., 2015).

Transformations

Regarding the neuroimaging data, preprocessing will be carried out with the Statistical Parametric Mapping software package (SPM12; Wellcome Trust Centre for Neuroimaging, UCL, London, UK) using standard algorithms and parameters (slice timing correction, VDM

calculation from field maps, realign & unwarp, coregistration, segmentation, functional and structural normalization and smoothing). Region of Interest (ROI) analyses will be based on ROIs from independent datasets (such as the meta-analysis data of Lamm et al. (2011), and the preceding 'placebo empathy analgesia' study by Rütgen, Seidel, Silani, et al., (2015).

Follow-up analyses

Significant interactions, if not sufficiently explained by the analysis plan and in particular by the planned comparisons, will be followed-up (and corrected for multiple comparisons).

Inference criteria

All analyses will be run one-tailed because of specific a-priori defined, directional hypotheses. Regarding the behavioral analyses, we will use an alpha level of 0.05 and a 95 % confidence interval for determining if the statistical tests suggest that the results are significantly different from those expected if the null hypothesis were correct. Regarding the analysis of the imaging data, we will use multiple comparison correction using Random Gaussian Field Theory, as implemented in SPM12.

Data exclusion

In general, outliers (defined as values greater than 3 standard deviations from the mean) will not be included in the analysis. Participants who delivered ratings in less than 60 % of all trials in each condition, or whose ratings were erratic/seem random (e.g., inconsistently reflecting pain vs. no pain conditions) will be excluded. Additional exclusion criteria are expressed doubts about the setup of the study, low belief scores regarding the effectiveness of the placebo treatment and strong decreases between the first and second medication effectiveness measure, as well as three or more needed conditioning repetitions (see above for a thorough description of placebo non-responder identification).

If subjects show consistent extensive movement during the fMRI scans, and in particular, if this movement is stimulus-related, they will be excluded from further analysis.

Missing data

If a subject rated in less than 60% of all trials in at least one of the conditions, that subject will not be included in the analyses including the affected condition. All other subjects with missing or incomplete data (e.g., regarding the questionnaires or missing values in single trials) will not be excluded from the analysis.

Exploratory analysis

We expect that certain demographic or personality traits may be related to first-hand and empathy for pain on the behavioral and neural level. Therefore, we will look for relationships between sociodemographic and trait variables (gender, empathy, vicarious pain, first-hand pain processing, depression, autistic traits, alexithymia) and post-experimental ratings of the other participant (e.g., similarity, liking, attributed strength, neediness, and agreeableness), and the primary outcome measures of empathy for pain (pain/unpleasantness ratings and neural activation).

After the scanning session, we will also assess previous experiences and associations with medical pain-reducing gels / basic skin creams. Furthermore, we will investigate Experimenter-Effects (Rosenthal, 1976) by asking about expectations regarding the results at the end of the session (whether the participants had any expectations or what expectations he/she thinks the experimenters of the study had).

We will also check whether the ratings regarding the effectiveness of the placebo treatment pre- and post-conditioning as well as post-session changed significantly.

Finally, we want to explore other analysis methods of the functional imaging data, especially regarding (1) the temporal dynamics of the BOLD-response, (2) habituation effects and (3) effective connectivity between different ROIs. Regarding (1), we aim to employ ROI-based time series analysis and whole-brain GLM by means of a Finite Impulse Response Model (FIR; Glover, 1999) to account for potential variability in the time course of the

evoked BOLD response and spontaneous brain network activity (Fox et al., 2006). For (2), we will compare different time points/events that happen earlier vs. later in the two tasks to check for significant differences relating to habituation to the task/stimuli. Finally, regarding (3) we want to conduct Dynamic Causal Modelling (DCM; e.g. Friston et al., 2019) to investigate effective connectivity with self vs. other and control vs. placebo as modulators.

Summary

Provide a narrative summary of what is contained in this registration, or how it differs from prior registrations.

This is an addendum to the preregistration of this project, uploaded on August 3rd 2018. There, we wrote: "Non-responders will be determined by procedures similar to the ones used in Rütgen, Seidel, Silani, et al. (2015). In short, a combination of three measures will be used: First, we will record any verbally expressed doubts about the analgesic effects of the gel or pain medication in general as well as about the study setup after the experiment by means of feedback questions. If a participant expresses doubts in any of these domains, we will ask him or her to elaborate these doubts further. Second, differences of the belief scores about the effectiveness of the placebo gel before and after the placebo induction procedure as well as at the end of the session will be analyzed. Exceptionally low total belief scores and strong decreases between first and second measure (pre and post placebo induction) will serve as a measure for lack of responding. Third, we will take the number of placebo conditioning trials into account. If participants respond with a value greater than 5 on a 9-point rating scale from 0 = 'not noticeable' to 8 = 'extremely painful, but bearable' to the conditioning stimulus (delivered at a medium intensity of 4-5), we will deem the conditioning trial as non-successful, wait another 2 minutes for the medication to take effect, and then try again. This will be repeated for a maximum of four times until participants respond with values of 1-5 to

the conditioning stimulus. If three or more such repetitions are necessary, this will be taken as an indication of non-responding to the placebo treatment."

In this context, we wish to disclose an additional exclusion criterion regarding non-responders to the placebo manipulation that we unfortunately omitted to mention in the original preregistration: As a fourth measure of identifying non-responders, we will use the actual first-hand pain ratings of the left and right hand. Average ratings (calculated by subtracting the control stimuli from the pain stimuli values: pain - no pain) of the right hand (where the placebo gel was applied) that are higher or equal to ratings on the left hand (control hand) will be deemed as an indicator of non-responding. This additional measure was not possible in the prior study by Rütgen, Seidel, Silani, et al. (2015) due to a between-subjects design with a placebo and a control group. In our study, however, each subject's left hand acts as the subject's own control. We will therefore use the originally preregistered three measures and the additional fourth measure mentioned here to identify and exclude non-responders of the placebo manipulation.

The data collection of this project is currently ongoing, and we have not started analyzing at the data yet. We recently noticed this omission and wanted to disclose it as soon as possible by adding it to the preregistered plan before beginning with data inspection and analysis.

3.2 Study 1: Another's pain in my brain: No evidence that placebo analgesia affects the sensory-discriminative component in empathy for pain

Helena Hartmann[a], Markus Rütgen[a], Federica Riva[a], & Claus Lamm[a*]

[a] *Social, Cognitive and Affective Neuroscience Unit, Department of Cognition, Emotion, and Methods in Psychology, Faculty of Psychology, University of Vienna, Vienna, Austria*

* *Corresponding author*

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3.2.1 Highlights

- Investigated placebo modulation of somatosensory and affective components of pain.
- Localized placebo analgesia effects for self-report and fMRI of first-hand pain.
- No evidence for a transfer of those effects to empathy for pain.
- Suggests that somatosensory sharing does not play a critical role in pain empathy.

3.2.2 Abstract

The shared representations account of empathy suggests that sharing other people's emotions relies on neural processes similar to those engaged when directly experiencing such emotions. Recent research corroborated this by showing that placebo analgesia induced for first-hand pain resulted in reduced pain empathy and decreased activation in shared neural networks. However, those studies did not report any placebo-related variation of somatosensory engagement during pain empathy. The experimental paradigms used in these studies did not direct attention towards a specific body part in pain, which may explain the absence of effects for somatosensation. The main objective of this preregistered study was to implement a paradigm overcoming this limitation, and to investigate whether placebo analgesia may also modulate the sensory-discriminative component of empathy for pain. We induced a localized, first-hand placebo analgesia effect in the right hand of 45 participants by means of a placebo gel and conditioning techniques and compared this to the left hand as a

control condition. Participants underwent a pain task in the MRI scanner, receiving painful or non-painful electrical stimulation on their left or right hand, or witnessing another person receiving such stimulation. In contrast to a robust localized placebo analgesia effect for self-experienced pain, the empathy condition showed no differences between the two hands, neither for behavioral nor neural responses. We thus report no evidence for somatosensory sharing in empathy, while replicating previous studies showing overlapping brain activity in the affective-motivational component for first-hand and empathy for pain. Hence, in a more rigorous test aiming to overcome limitations of previous work, we again find no causal evidence for the engagement of somatosensory sharing in empathy. Our study refines the understanding of the neural underpinnings of empathy for pain, and the use of placebo analgesia in investigating such models.

3.2.3 Introduction

Empathy is a multifaceted psychological construct fundamental for human social interactions and relationships (e.g. Marsh, 2018 for recent review). While many definitions of empathy have been proposed, here we define empathy as an affective state isomorphic to the state of another person, encompassing a partial and experiential sharing of that person's affect (Hall & Schwartz, 2019; Lamm et al., 2019 for overviews). Studies in recent years have already brought considerable advances in our understanding of the neural mechanisms underlying empathy (de Vignemont & Singer, 2006; Keysers & Gazzola, 2006; Lamm et al., 2019; Lockwood, 2016; Marsh, 2018; Preston & de Waal, 2002 for reviews; Jauniaux et al., 2019; Lamm et al., 2011 for meta-analyses). According to one influential account, the shared representations account, the experience of another individual's emotion recruits neural processes that are (partially) functionally equivalent to those engaged during the first-hand experience of that emotion (Bastiaansen et al., 2009; Lamm et al., 2016; Lamm & Majdandžić, 2015 for reviews). In other words, we reactivate and use our own emotion

system in order to simulate another's emotional state and, in turn, are able to empathize because we share the representation of that emotion. For example, observation of pain in another individual directly triggers activation of matching neural substrates in the observer also related to first-hand pain processing through which the pain of the other can be understood. Yet, apart from some general debate on the validity of this account (Zaki et al., 2016 for a review; but see also Zhou, Li, Zhao, Xu, Zheng, Fu, Yao, et al., 2020a for a recent preprint), there exists an explanatory gap regarding the relative contribution of somatosensory, compared to affective, brain regions to empathy.

Pain is widely used to study the neural underpinnings of empathy (Fan et al., 2011; Jauniaux et al., 2019; Lamm et al., 2011; Timmers et al., 2018 for meta-analyses). Classical first-hand pain processing is subdivided into two distinct brain networks, whose related brain activities map onto the first-hand experience of pain (Osborn & Derbyshire, 2010; Ploner et al., 2002; Jauniaux et al., 2019 for a meta-analysis; Tracey & Mantyh, 2007; Zaki et al., 2016 for reviews). Primary and secondary somatosensory cortices (S1/S2) encode information related to sensory-discriminative features of pain, such as location, timing or physical characteristics (Keysers et al., 2010; Vierck et al., 2013 for reviews). In turn, activity in anterior/midcingulate cortices (ACC/MCC) and anterior insula (AI) has been associated with affective-motivational aspects of pain, such as its subjective unpleasantness (Lockwood, 2016 for a review; Singer et al., 2004). While activation associated with the sensory-discriminative component is usually represented contralateral to the location of an applied stimulus (especially for S1, but also S2; Bingel et al., 2004; Haggard et al., 2013; Ogino et al., 2005; Omori et al., 2013; Ritter et al., 2014), this has not been reported for the affective-motivational component (Lamm et al., 2011 for a meta-analysis). Apart from pain per se, aMCC or AI are also activated by many other processes, such as conflict monitoring, executive control or salience processing (Eisenberger, 2015 for a review; Liang et al., 2019).

There is an ongoing debate about the specificity of those regions that challenges the so called "pain matrix" and describing regions such as aMCC and AI as being modality-specific to pain (see also Lieberman & Eisenberger, 2015; Wager et al., 2016 for a critical discussion around the dorsal ACC/aMCC). In line with this argumentation, activity in this network could also represent a more basic domain-general mechanism where significant events regardless of the sensory channel are detected (Borsook et al., 2013; Legrain et al., 2011 for reviews).

In addition, the relative importance of each component, and specifically the contribution of somatosensory processing to empathic pain experiences, remains controversial. Numerous fMRI and EEG studies have demonstrated that receiving pain oneself and empathizing with another person in pain recruit overlapping activation in both of these pain processing components, providing possible evidence for shared representations (Lamm et al., 2011 for a meta-analysis; see Singer & Frith, 2005; Singer & Lamm, 2009 for reviews). For example, many studies continuously observed this overlap in bilateral AI and anterior MCC (aMCC), speaking for the affective-motivational component as the "core" of pain empathy processing (e.g. Benuzzi et al., 2018; Corradi-Dell'Acqua et al., 2011; Jackson et al., 2005; Singer et al., 2004; see Ding et al., 2019; Jauniaux et al., 2019 for meta-analyses). In addition, others reported overlapping activation in sensorimotor and somatosensory brain areas, highlighting the importance of the sensory-discriminative component for empathic pain experiences (e.g. Avenanti et al., 2005; Bufalari et al., 2007; Gallo et al., 2018; Lamm, Nusbaum et al., 2007; Motoyama et al., 2017; Nummenmaa et al., 2008; see Riečanský & Lamm, 2019 for a review). Interestingly, results regarding the latter have only been reported when using picture-based empathy for pain paradigms, where explicit visual stimuli of others in pain are used to elicit empathic responses.

To test the role of brain areas underpinning empathic responses more specifically and go beyond correlational evidence for shared activations, causal methods, such as

psychopharmacological manipulations, have recently been used (Gallo et al., 2018). Placebo analgesia has been shown to reliably reduce first-hand pain using global (orally administered pill) or local (topically applied gel/cream) manipulations with no active pharmacological compound (Amanzio et al., 2013 for a meta-analysis; Benedetti & Piedimonte, 2019; Colloca et al., 2013; Wager & Atlas, 2015 for reviews; Corsi & Colloca, 2017). Rütgen, Seidel, Silani, et al. (2015) argued that if empathy for pain is indeed directly grounded in the experience of first-hand pain, placebo analgesia should also result in decreased empathy for pain. In three consecutive studies, they observed reduced self-reported empathy in participants in whom placebo analgesia had been induced (Rütgen, Seidel, Riečanský, et al., 2015; Rütgen, Seidel, Silani, et al., 2015; Rütgen et al., 2018). These results were later replicated by another group of researchers using the painkiller acetaminophen (Mischkowski et al., 2016). Imaging and EEG data further showed diminished activation during empathic pain processing in areas coding for the affective-motivational component (Rütgen, Seidel, Silani, et al., 2015) as well as reduced amplitudes of P2, an event-related potential (ERP) component (Rütgen, Seidel, Riečanský, et al., 2015; Rütgen et al., 2018). This component indexes neural computations related to the affective pain processing network and possibly also to somatosensory processing, as indicated by source localization studies (Cruccu et al., 2008; Perchet et al., 2012).

While these results suggest that empathy for pain is grounded in similar neural processes as first-hand pain (but see Lamm et al., 2019 and Zaki et al., 2016 for critical discussions), they also indicate that this neural sharing might only be partial and limited to a sharing of *affective* processes and representations. This brings back to the fore the unresolved issue about the role of the sensory-discriminative component in pain empathy (Fabi & Leuthold, 2017; Lamm, Nusbaum, et al., 2007; Loggia et al., 2008; Riečanský & Lamm, 2019 for a review; Singer et al., 2004). One line of research investigating patients with congenital

insensitivity to pain (CIP) who display an impairment in their own somatosensory processing showed that these patients exhibit comparable dispositional empathy, activate affective brain areas such as aMCC and AI in response to other's pain, and do not differ from control participants without CIP in those responses (Danziger et al., 2006, 2009). This has been found using again picture-based paradigms and suggests that somatosensory "mirror matching" of the other's with one's own state might not be necessary for those patients in order to empathize. However, those studies also found more variable and lower pain intensity ratings to pictures of others in pain compared to controls, suggesting that patients with CIP might underestimate other's pain.

The previous studies from our lab also did not report any variation in somatosensory activation by placebo analgesia, even when lowering statistical thresholds (Rütgen, Seidel, Riečanský, et al., 2015; Rütgen, Seidel, Silani, et al., 2015). This is surprising, given that placebo analgesia generally affects both components in first-hand pain (Benedetti et al., 2005; Wager & Atlas, 2015 for reviews). However, the experimental paradigm used in these studies may not have been tailored to provoke the engagement of somatosensory processes in the empathic experience, making their potential modulation by placebo induction difficult to discern (Keysers et al., 2010; Lamm et al., 2011). In fact, it has been suggested that *picture-based* empathy for pain paradigms directing the (visual and principal) attention of participants to the specific body part in pain, might be required to observe activation in somatosensory areas (e.g. visual input of a needle penetrating the hand; Timmers et al., 2018; Xiang et al., 2018 for overviews). Previous studies, however, employed a *cue-based* task, where facial expressions and abstract cues (Rütgen, Seidel, Silani, et al., 2015) or only abstract cues (Rütgen, Seidel, Riečanský, et al., 2015; Rütgen et al., 2018) indicated electrical stimulation given to the participants themselves or a second person. It has also been shown that the type of stimuli and the context are a strong driver of brain activation (Gu & Han,

2007; Han et al., 2009). Thus, the task may not have been sufficiently sensitive to detect somatosensory modulation.

In this preregistered study, we therefore aimed to a) replicate the results of our previous study regarding shared representations in the affective domain (Rütgen, Seidel, Silani, et al., 2015), and b) clarify the contribution of somatosensory processing in empathy for pain using an experimental paradigm allowing us to overcome the potential limitations of our previous research. To this end, we combined a causal experimental manipulation, consisting of a localized induction of placebo analgesia, with a paradigm putting a stronger emphasis on somatosensory aspects of the (empathic) pain experience than previous paradigms. More precisely, placebo analgesia was induced for one hand only, and participants' attention was more specifically directed to the targeted hand than in previous tasks using more abstract cues, rather than the visual depictions of the hands and the instruction to infer the other's experience from those depictions used here. In other words, we specifically optimized the study design in a way to maximize sensitivity for a potential placebo-driven modulation of somatosensory brain activity.

This motivated the following preregistered, directional hypotheses: First, we predicted reductions in first-hand and empathy for pain as well as unpleasantness ratings for the right hand, where placebo analgesia was induced, compared to the left hand acting as a control. Second, we hypothesized that the sensory-discriminative component of pain empathy would be modulated in a similar fashion by placebo analgesia as the affective-motivational component – i.e., that neural responses related to the right hand would be reduced in S1 and S2 compared to the left hand – and that this would trigger correspondingly reduced neural responses in bilateral AI and aMCC.

3.2.4 Materials and Methods

Data and Code Availability Statement

The data was newly acquired for the present study. Unthresholded statistical maps will be made available via an online repository upon acceptance and stimuli templates for the pain task are uploaded within the Open Science Framework (OSF) project (osf.io/2q3zu/).

Preregistration

We report how we determined our sample size, all data exclusions, all manipulations, and all measures in the study. This study was preregistered on the OSF prior to any creation of data (Hartmann et al., 2018; preregistration: osf.io/uwzb5; addendum: osf.io/h7v9p) and was designed to extend and specify the results of Rütgen, Seidel, Silani, et al. (2015) in regard to somatosensory sharing. Methods reported below are therefore reproduced partly verbatim from the preregistration. Note that the preregistered plan contains a second research question that is not part of the present paper but will be reported elsewhere. In the following methods and results, we clearly distinguish preregistered procedures and analyses from those added post hoc.

Participants

Participants were recruited by means of flyers and online advertising in Vienna, Austria and via an existing database of study participants. Upon interest, they were screened by means of an online questionnaire (see A.1 in Supplement A for detailed information regarding exclusions). An *a priori* power analysis using G*Power 3 (Faul et al., 2007) was conducted using a conservative average of the lowest effect sizes from previous placebo empathy analgesia studies (one-tailed paired *t*-test, Cohen's d = .79 to .44 for self-report and .40 to .39 for affective brain areas; Rütgen, Seidel, Riecansky, et al., 2015; Rütgen, Seidel, Silani, et al., 2015) to calculate the needed sample size to detect a medium effect size of d = .40 at a standard error probability of $\alpha = .05$ with a power of $1\text{-}ß = 0.8$. This yielded a sample

size of 41 participants. However, considering that the modulation of placebo analgesia might not be equal for somatosensory compared to previously reported affective brain regions, a total of 45 placebo responders was set as the stopping-rule. The exclusion of nonresponders in regard to the placebo manipulation was crucial to obtain a sample of participants showing a robust localized, first-hand placebo analgesia effect, in order to investigate a transfer of this effect to empathy. We originally included three measures to identify nonresponders in our preregistration, as per the criteria in Rütgen, Seidel, Silani, et al. (2015) who used a similar placebo analgesia induction and a cue-based task: a) Doubts about the study setup, b) low beliefs regarding the effectiveness of the "medication", and c) too many unsuccessful conditioning trials (for a thorough description of the non-responder criteria, see supplement A.2). During data collection, we uploaded an addendum to include a fourth measure we had previously overlooked, the direct comparison of self-related pain ratings of the right and left hand. This measure was not possible in the previous study we oriented our procedures on but was added due to our within-subjects design in order to better identify nonresponders, maximize the placebo responsiveness of the final sample and bolster the interpretability of our results. We had not observed or analysed any of the collected data when preregistering this addendum. Importantly, this was also the criterion that identified almost all of the nonresponders. We excluded 20 participants (25.6%) for not responding to the placebo manipulation (according to a-priori criteria set above), seven due to technical malfunctioning of the pain stimulator, five for inconsistent ratings (e.g., similar ratings for painful and non-painful conditions independent from the placebo manipulation) and/or extensive movement and one due to a spontaneously found abnormality in the brain, adding up to a total of 78 recruited participants.

Our final sample included 22 males and 23 females (Age: $M \pm SD = 23.84 \pm 2.73$ years, range = 19-32; all right-handed with laterality quotients (LQs) ≥ 80 and normal or corrected-

to-normal vision). We purposefully recruited only strongly right-handed participants and did not counterbalance the location where placebo analgesia was induced between participants to avoid laterality problems in our fMRI analyses, as well as to increase sample homogeneity and comparability of the induction procedure. Participants had mean trait empathy scores as measured with the four subscales of the Interpersonal Reactivity Index (IRI; Davis, 1980) that were within the typical range reported by Davis (1980).

Before the commencement of the study, five pilot participants were tested to confirm the existence of a localized, first-hand placebo analgesia effect and improve study procedures, but these datasets were not included in the final sample. All participants gave written consent at the outset of each session. The study was approved by the ethics committee of the Medical University of Vienna (EK-Nr. 661/2011) and performed in line with the latest revision of the Declaration of Helsinki (World Medical Association, 2013).

Procedure

The study consisted of two parts: First, participants came alone for a one-hour session to the lab, where they filled out questionnaires on a computer, and had photos of their hands taken that were used as individualized stimulus material for the scanning session. After an average interval of 32.86 ± 29.16 (*M* ± *SD*) days, participants came to the MRI scanner where they took part in the main experiment. Each one arrived together with a second person (who was a female confederate of similar age invited by the experimenters acting as a second participant, as per Rütgen, Seidel, Silani, et al., 2015). The experimenter explained to both that the goal of the study was to investigate brain activity associated with a local anesthetic in the form of a medical gel. Furthermore, it was made clear that only one person, i.e., the participant, would receive this medication on the right hand and complete the tasks inside the scanner, while the confederate would not receive any medication and complete the same tasks on a computer next to the scanner. We took great care in creating a social situation in order to

foster a friendly environment where it was easy to empathize. This was done by a) having a confederate present, b) letting participant and confederate interact at multiple time points during the session and complete the tasks together in the same room, c) always addressing both participants over the intercom when talking to them in between tasks, and d) telling the participants that their answers would be completely confidential.

After signing the consent form and the MR-safety questionnaire, the confederate was asked to wait outside the control room while an individual psychophysical pain calibration was performed with the participant. This was done to determine the maximum level of tolerable pain and to specify average subjective values for very painful (rating of 7 on a scale from 0 = not painful to 8 = extremely painful), medium painful (rating of 4) and not painful, but perceivable (rating of 1) stimulation. As pain tolerances can vary depending on the body part and handedness (Murray & Safferstone, 1970; Pud et al., 2009), we calibrated each hand individually to match the stimulation intensities and subjective pain levels for each hand. The hand calibrated first was counterbalanced across participants. To this end, an electrode was attached to the dorsum of each hand using medical tape. Electrical stimulation of various strengths (stimulus duration = 500 ms) was administered using the procedure employed by Rütgen, Seidel, Silani, et al. (2015), with two rounds going from very low (0.05 mA) to continuously higher stimulation until the participant indicated the last received stimulus as an '8', after which each round was terminated. This was followed by a third round of stimuli with random intensity in the before calibrated range. Short breaks between the stimuli and longer breaks of a few minutes between the rounds ensured an independent rating of each stimulus unbiased by previous one(s). Participants were instructed to rate each stimulus as intuitively but also as accurately as possible. Input intensities for the task were the individual average ratings for painful (rating of 7) and non-painful (rating of 1) stimulation given during calibration, separately for the left and right hand. Those were 0.64 ± 0.67 ($M \pm SD$) mA (left

hand) and 0.53 ± 0.36 mA (right hand) for painful, and 0.09 ± 0.06 mA (left hand) and 0.10 ± 0.06 mA (right hand) for non-painful sensations. We compared values for painful and non-painful stimulation separately for left and right hands using two paired *t*-tests in order to investigate differences in pain tolerance between the hands (analysis not preregistered; Murray & Safferstone, 1970; Pud et al., 2009). Stimulation intensities did not differ between the two hands (pain: $t(44) = 1.59$, $p = .117$; no pain: $t(44) = -0.99$, $p = .325$). In general, electrical stimulation was delivered using a Digitimer DS5 Isolated Bipolar Constant Current Stimulator (Digitimer Ltd, Clinical & Biomedical Research Instruments).

Next, a medical student in a white lab coat posing as the study doctor introduced the medication as a "powerful local anesthetic" and gave information on its effects and possible side effects. Participants were told that the medication would be effective after a 15–20-minute waiting period and then remain stable for 2-3 hours. The study doctor attached a white paper bracelet to the right wrist of the participants (as a visual reminder which hand received the "medical treatment"), then applied and rubbed in the placebo gel on the dorsum of the right hand. On the left hand, participants were told that a control gel with no active ingredients was applied. In reality, both gels contained nearly the same basic ingredients of a standard skin gel with no active pharmacological components (see A.3 in Supplement A for exact ingredients). In matching the two gels, we aimed for clearly recognizable visual and olfactory distinction, but the same tactile feeling and hydrating properties, and adhered to previously used procedures inducing placebo analgesia with topical creams and gels (Benedetti et al., 1999; Bingel et al., 2006; Geuter et al., 2013; Schenk et al., 2014; Tinnermann et al., 2017). After the application, the participant was led outside the control room to (ostensibly) wait for the "medication" to take effect and was told that the confederate would undergo the same pain calibration in the meantime. During the waiting period, the participant was instructed regarding the pain task. Importantly, it was stressed to the

participant that the experimenters or the confederate would not observe their answers at any time and there was no right or wrong when answering. This was done to avoid or reduce socially desirable responding.

After 15 minutes, the participant returned to the control room and was told that the effectiveness of the medication would now be verified using a "pain test". Here, we employed a classic conditioning procedure to amplify the effects of the placebo. After removal of excess gel and disinfection with 70% isopropyl rubbing alcohol, one electrode was again attached to the dorsum of each hand, using the same placement as during calibration. Participants were told that they would be getting stimulation on both hands that they had judged as "painful" before and were asked to rate how painful it felt for them. On the left (control) hand, participants indeed received stimulation with a prior subjective rating of 7 ("very painful"), on the right (placebo) hand, however, they covertly received stimulation with a prior rating of 4 ("medium painful") to suggest substantial pain relief by the medical gel. All participants completed at least two conditioning rounds (in the first round, three successive stimuli were given, in subsequent rounds four), and were given oral feedback after each round by the experimenter, namely that their ratings on the left/control hand were similar to their ratings during calibration, but the ratings on the right/placebo hand had decreased substantially. If participants rated the stimuli on the right/placebo hand greater than 5 and/or the stimuli on the left/control hand lower than 5, the conditioning round was deemed unsuccessful and repeated up to a maximum of four times. After unsuccessful rounds, stimuli were slightly adjusted for the next round(s) to increase the contrast between the two hands, i.e., increasing intensities for the left hand and/or decreasing intensities for the right hand. This was done without knowledge of the participants, who thought they received the same level of stimulation on both hands at all times.

Afterwards, the participant and the confederate were both led into the scanner room and the confederate was seated by a table with a computer screen, keyboard, and headphones next to the scanner. During the scanning, the confederate was therefore sitting next to the MR scanner, but not in direct sight of the subject. Following general adjustments, the participant completed two runs (22 minutes each) of the pain task, and one run of another task (not reported here) in a fixed order. The rating hand of the participants was counterbalanced between but kept constant within participants over all tasks. Upon completion of all tasks, the experimenter went inside the scanner room pretending to get the confederate, after which the field map and structural image were acquired. After scanning, participants filled out post-experimental questionnaires. They received a compensation of 50 Euros for taking part in the whole study and an aliquot amount if they dropped out earlier. The overall scanning session took ~ 4 hours, of which participants spent around 80 minutes lying in the scanner.

Pain task

To induce pain, we used short-lasting painful and non-painful electrical stimulation delivered to the right and left hands of the participant or confederate in different trials. By adding a non-painful stimulation, we aimed to control for domain-general aspects (such as generalized perceptual or behavioral responses, including stimulus-directed attention) related to stimulus presentation (Petrovic et al., 2002; Rütgen, Seidel, Silani, et al., 2015). The pain task was implemented in MATLAB R2017b (Mathworks, 2018) using the Cogent 2000 Toolbox Version 1.33 (http://www.vislab.ucl.ac.uk/ cogent_2000.php). Participants saw either pictures of their own hands (with the right/placebo hand wearing a white bracelet) or the confederate's hands from an egocentric perspective on black background, depending on who would receive the next stimulation (see Figure 1 and A.4 in Supplement A). By combining first-hand and empathy for pain in one task, participants should have a clear representation of how the electrical stimulation of the other's hand would feel, which, in turn,

should amplify the empathic response. Each trial began with the written German words "DU" ("YOU", self-trials) or "SIE" ("HER", other-trials) in either red or blue (for painful or non-painful stimulation, respectively), indicating the target and the intensity of the next stimulation (target cue; 2000 ms).

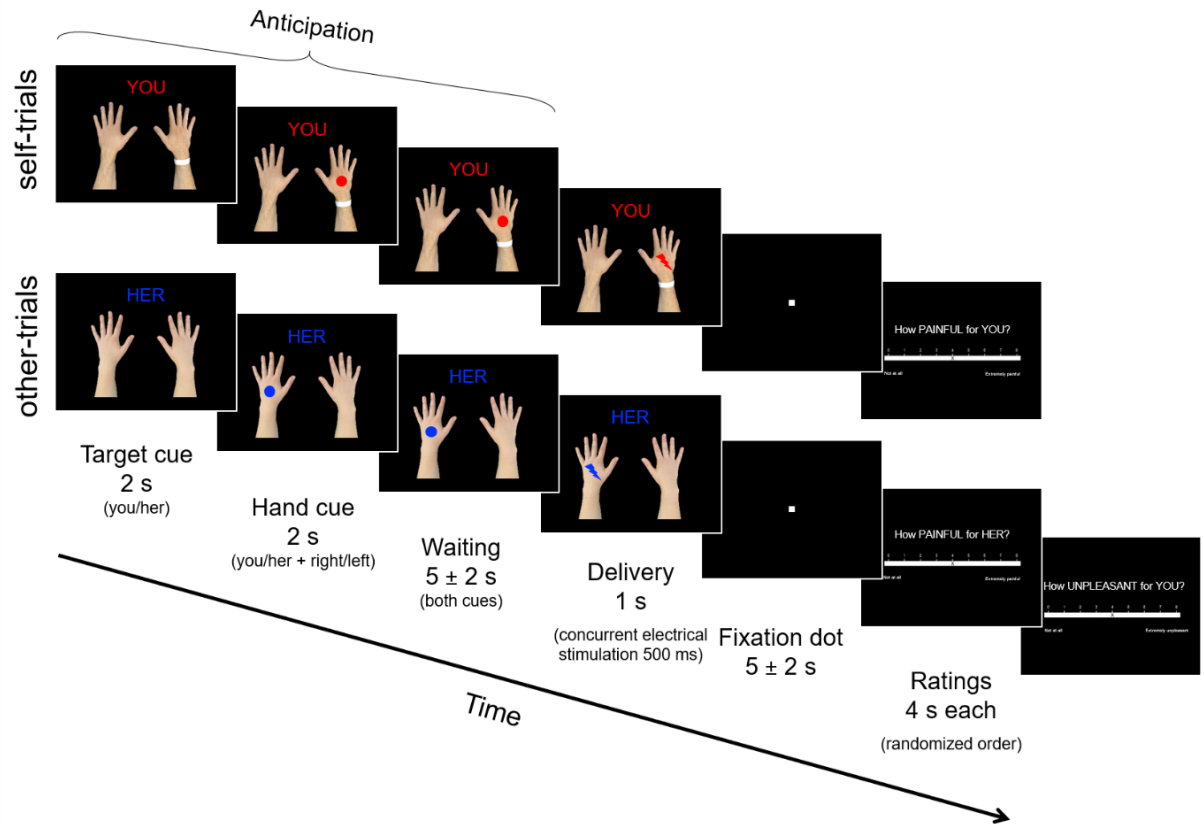


Figure 1. Overview of the pain task. As part of a 2x2x2 full-factorial design, participants either received painful (red icons) or non-painful (blue icons) electrical stimulation themselves (seeing their own hands; self-trials) or witnessed a second person receiving such stimulation (seeing the confederate's hands; other-trials). Prior to the task, all participants had undergone a localized placebo analgesia induction on their right hand, while the left hand acted as each participant's individual control. In half of all trials, subjective ratings were collected after stimulus delivery for self- and other-related pain intensity, as well as self-related unpleasantness when observing the other person in pain. Figure taken from Hartmann, Rütgen, Riva, et al. (2021).

Then, a circle icon in the same color of the word was shown on the hand receiving the next stimulation (hand cue; 2000 ms). A jittered waiting period (5000 ± 2000 ms, evenly distributed in 500 ms steps) simultaneously displaying the hands with the two cues followed. The two cues and the waiting phase can all be described as the anticipation period, although only with the hand cue, participants had all information they needed for the next trial. Then, the circle changed into a lightning icon of the same color, indicating stimulus delivery

(duration of electrical stimulus = 500 ms, display of delivery cue = 1000 ms). This was followed by a jittered waiting period (5000 ± 2000 ms, evenly distributed in 500 ms steps), depicting a white dot on black background. In half of all trials, stimulation delivery was followed by a rating period (4000 ms per question; appearance of the rating phase was determined by four pseudorandomized sequences previously created). During self-trials, participants were asked how painful the stimulus had felt for them. During other-trials, participants were asked two questions tapping into different aspects of empathy (Coll et al., 2017; Lamm & Majdandžić, 2015), namely (1) how painful the stimulus was for the other person (cognitive-evaluative aspect) and (2) how unpleasant it was for the participant him- or herself to witness the other person receiving such stimulation (affective-sharing aspect). The two empathy questions always appeared in a random order. Questions were rated on visual analogue scales from 0 = "not perceivable at all" to 8 = "extremely painful/unpleasant". A 2000 ms inter-trial-interval screen depicting a white dot on black background was shown before the start of the next trial. Participants completed 128 trials with an average duration of 21/25 s (self-trials/other-trials) per trial, 64 trials per run and 16 trials per condition, with trials appearing in one out of four pseudorandom orders previously created. Importantly, by introducing the two long jitters and randomizing conditions in a way that no condition appeared more than once in a row, we ensured sufficient spacing of especially first-hand pain trials and thus avoided habituation to the stimuli. Furthermore, painful and non-painful stimulation was given at two separate hand locations to avoid carry-over effects, especially from the pain to the no-pain conditions. Post hoc analyses of first-hand pain ratings over the course of the experiment also did not reveal any signs of habituation (data not shown).

MRI data acquisition

MRI data was acquired using a 3 Tesla Siemens Magnetom Skyra MRI-system (Siemens Medical, Erlangen, Germany), equipped with a 32-channel head coil. The functional scanning

sequence included the following parameters: Echo time (TE)/repetition time (TR) = 34/1200 ms, multi-band acceleration factor = 4, flip angle = 66°, interleaved multi-slice mode, interleaved acquisition, field of view = 210 mm, matrix size = 96×96, voxel size = 2.2×2.2×2.0 mm^3, 52 axial slices of the whole brain coplanar the connecting line between anterior and posterior commissure, and slice thickness = 2 mm. Functional volumes were acquired in two runs (and one run for another task), with small breaks in between the three runs. Structural images were acquired using a magnetization-prepared rapid gradient-echo sequence (TE/TR = 2.43/2300 ms, ascending acquisition, field of view = 240 mm, single shot multi-slice mode, 208 sagittal slices, voxel size = 0.8×0.8×0.8 mm^3, flip angle = 8°, slice thickness = 0.8 mm).

Behavioral data analysis

The analysis workflow of the behavioral and fMRI data is summarized in Figure 2 and referred to throughout the following methods and results. Statistical analyses were performed in RStudio Version 3.6.1 (R Core Team, 2020; for analysis and plotting functions see A.5 in Supplement A). We conducted all our preregistered *t*-tests one-tailed due to *a priori* directional hypotheses.

Preregistered analyses. We implemented a within-subjects, full-factorial design with three factors of two levels each (*treatment*: placebo vs. control hand, *target*: self vs. other, *intensity*: pain vs. no pain). Two parametric repeated-measures analyses of variance (ANOVAs) were used to analyze the results. In the first ANOVA (analysis A1 in Figure 2), the dependent variable was the self- and other-related pain ratings. A second ANOVA (analysis A2 in Figure 2) included the unpleasantness ratings as the dependent variable (omitting the factor *target*, as unpleasantness ratings were only collected in the empathy condition). For each ANOVA, we then computed planned comparisons using paired *t*-tests.

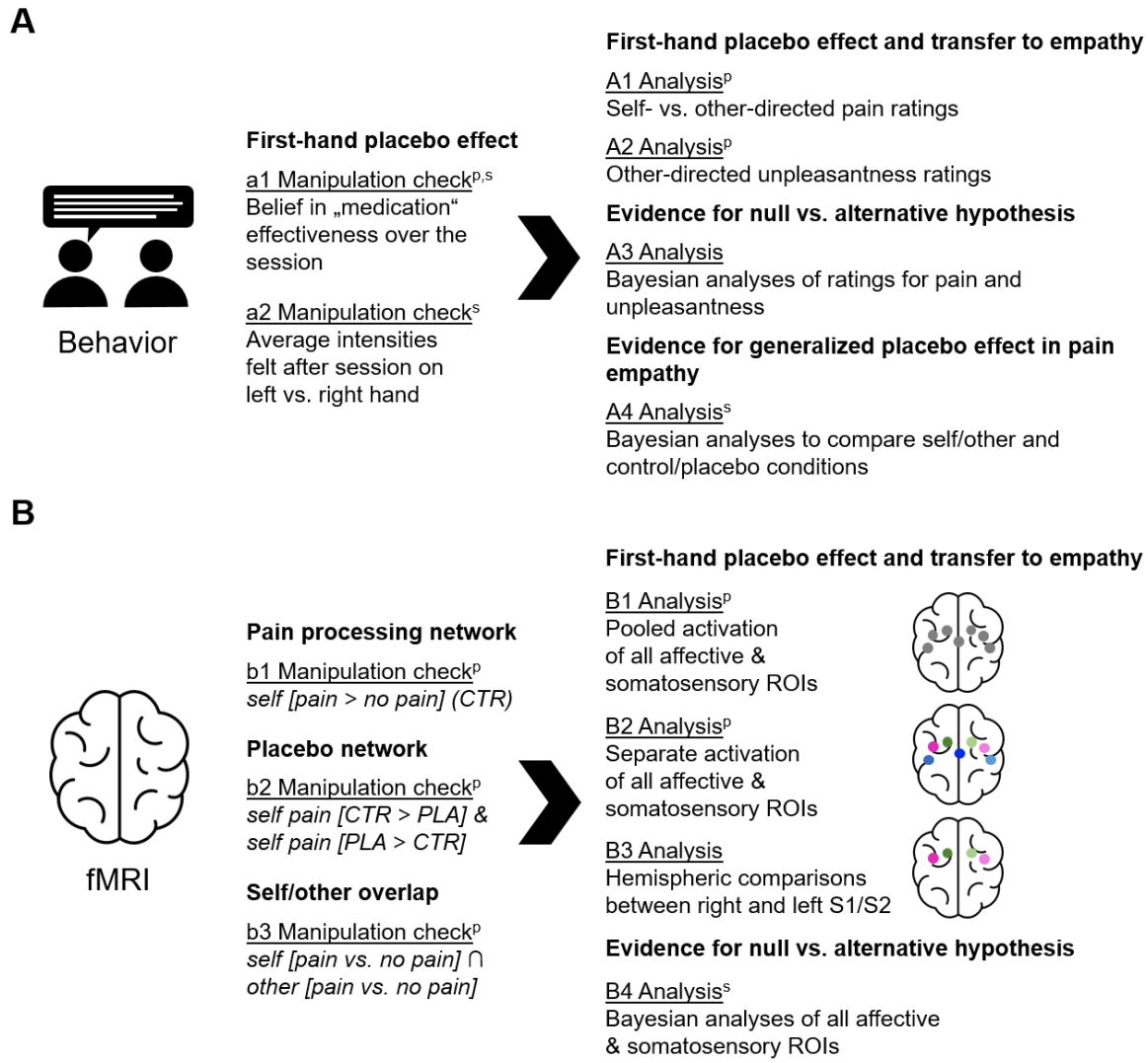


Figure 2. Overview of the analysis workflow. A) For the behavioral data, we explored the validity of our design using two manipulation checks (a1+a2; reported in A.6 in Supplement A). Then, we conducted four analyses to evaluate the evidence for a first-hand localized placebo analgesia effect and a transfer of this effect to empathy using the ratings collected from the task (A1-A4; A4 is reported in Supplement B). B) Regarding the fMRI data, we used three manipulation checks to establish the validity of our pain task (b1), the typical placebo analgesia network (b2) and the previously reported self-other overlap in brain activity related to first-hand and empathy for pain (b3). For our main analyses, we employed a region of interest (ROI) approach to evaluate the evidence for a first-hand localized placebo analgesia effect and a transfer of this effect to empathy in seven ROIs: anterior midcingulate cortex, bilateral anterior insula, as well as bilateral primary (S1) and secondary somatosensory cortex (S2). This was first done using pooled activation of all ROIs (B1) and then analyzing each ROI separately (B2). Finally, we gathered further evidence for a first-hand localized placebo effect and absence of a transfer to empathy using a hemispheric comparison analysis (B3). Bayesian analyses of the fMRI data can be found in the supplement (B4). Preregistered analyses are marked with [p], analyses in the supplement are marked with [s]; PLA = placebo; CTR = control. Figure taken from Hartmann, Rütgen, Riva, et al. (2021).

Post hoc analyses. Due to the unexpected "null" finding of no transfer of the first-hand placebo effect to empathy, we aimed to gather further relative evidence for the null vs. the

alternative hypothesis, using a Bayesian approach (e.g. Wagenmakers et al., 2018). This was realized with three Bayesian paired *t*-tests (analysis A3 in Figure 2) mirroring the above preregistered analyses. We used a standard Cauchy (0,1) prior of 1 as the effect size (indicating a 50% chance to observe an effect size between -1 and 1; e.g. Rouder et al., 2009). Note that Bayesian *t*-tests produce a Bayes Factor comparing the relative evidence between the alternative and null hypothesis (BF_{10}, H_1 vs. H_0; Mac Giolla & Ly, 2019). In interpreting these values, a $BF_{10} < 3$ has been suggested to indicate weak evidence, a $BF_{10} > 3$ positive evidence, and $BF_{10} > 150$ very strong evidence for the alternative hypothesis (Jarosz & Wiley, 2014). Evidence for the null compared to the alternative hypothesis (BF_{01}, H_0 vs. H_1) was computed as $BF_{01} = 1/BF_{10}$. For an additional analysis exploring the existence of any placebo-related downregulatory effect in the empathy condition (analysis A4 in Figure 2) as well as results and discussion, see Supplement B.

fMRI data preprocessing and analysis

Preprocessing and first-level analysis. To preprocess and statistically analyze the fMRI data, the software Statistical Parametric Mapping (SPM12, https://www.fil.ion.ucl.ac.uk/spm/software/spm12/, Wellcome Trust Centre for Neuroimaging) running on MATLAB Version R2015b (Mathworks, 2018) was used. All brain regions were labelled with the SPM Anatomy toolbox version 2.15 (Eickhoff et al., 2005). Preprocessing of the functional volumes included slice timing (reference = middle slice; Sladky et al., 2011), realignment with the participant-specific field map, coregistration of structural and functional images, segmentation into gray matter, white matter (WM) and cerebrospinal fluid (CSF) tissues, spatial normalization, and spatial smoothing by convolution with an 8 mm full-width at half-maximum (FWHM) Gaussian Kernel. The first-level design matrix of each participant contained eight regressors for anticipation (combining target + hand cues), eight for delivery and one for all rating phases, leading to 17 regressors. The

different conditions were modeled in an event-related fashion (event duration = 0 seconds) and convolved with SPM12's standard canonical hemodynamic response function. Adhering to the procedure used in our previous study, we modeled the whole time phase from the onset of the target cue until one second after delivery onset, combining anticipation and delivery (Rütgen, Seidel, Silani, et al., 2015). Additional nuisance regressors included six realignment parameters and two regressors modeling WM and CSF for each of the runs (the latter two were extracted using the REX toolbox; Duff, Cunnington, & Egan, 2007). We excluded 1-2 trials in four participants from analysis post hoc due to technical malfunctioning of the pain stimulator (e.g., missing stimulation in a pain trial).

Manipulation checks. We preregistered three manipulation checks testing (i) the validity of our design, (ii) the success of the placebo analgesia induction and (iii) the existence of overlapping activation for first-hand and empathy for pain (manipulation checks b1-b3 in Figure 2). The global evaluation of those checks was the basis for proceeding to test the main research question. To this end, eight contrast images were created for each participant (these were not specified in the preregistration). We then calculated a full factorial model within a flexible factorial framework in SPM12 using the within-subjects factors *treatment* (placebo vs. control hand) and *condition* – combining the factors *target* (self, other) and *intensity* (pain, no pain) – as well as the between-subjects factor *subject*. We determined significance using cluster-level inference. To correct for multiple comparisons, we calculated the cluster extent threshold by means of "CorrClusTh.m", an SPM extension script (Thomas Nichols, University of Warwick, United Kingdom & Marko Wilke, University of Tübingen, Germany; http://www2.warwick.ac.uk/fac/sci/statistics/staff/academicresearch/nichols/scripts/spm/). In all three checks, we adhered to the analysis approach employed in our previous study (Rütgen, Seidel, Silani, et al., 2015) for better comparability.

First, we used the contrast *[self - pain > self - no pain]* of the control hand to evaluate whether our design robustly activated brain areas associated with pain processing as in previous studies (manipulation check b1 in Figure 2). This check is reported at a cluster probability of $p < .05$ (familywise-error (FWE)-corrected cluster-forming threshold of $k = 188$, initial cluster-defining threshold $p < .001$ uncorrected). This strict whole brain threshold was chosen because we expected extensive activation in this contrast. To pass this check, we expected to find general affective and somatosensory activation in regions typically activated by first-hand pain.

Second, we aimed at showing that the placebo analgesia induction activated a widespread network previously identified in placebo analgesia studies (manipulation check b2 in Figure 2; see e.g. Atlas & Wager, 2012 for a summary). Here we used small volume correction (SVC), with a threshold of $p < .05$ FWE-corrected at peak-level, on the contrasts *[self - placebo hand > self - control hand]* and *[self - control hand > self - placebo hand]*, using only the pain conditions (initial threshold: $p < .001$ uncorrected). The SVC approach used here was directly motivated by previous studies (e.g. Bingel et al., 2007; Eippert et al., 2009; Geuter et al., 2013; Wager et al., 2011; Zubieta et al., 2005) and chosen to maximize sensitivity of the analyses, increase comparability to analysis approaches used in previous studies and specifically investigate previously reported, placebo analgesia-related brain regions. We used exactly the same regions and sphere sizes investigated in our reference study (Rütgen, Seidel, Silani, et al., 2015). In accordance with these studies, we analyzed spheres around MNI coordinates used in the study by Rütgen, Seidel, Silani, et al. (2015), as this study's overall design closely matched the present one, and as this allowed us to compare data from within the lab ([±x, y, z]; size of sphere): Dorsolateral prefrontal cortex (DLPFC; [±36, 13, 39]; 15 mm), S2 ([±39, -15, 18]; 10 mm), insula (anterior [±33, 18, 6] and posterior [±44, -15, 4] part; both 10 mm), dorsal (dACC; [±3, 6, 36]; 10 mm) and rostral ACC (rACC;

pregenual [±10, 32, -8] and subgenual [±6, 30, -9] parts; both 10 mm), ventral striatum ([±9, 6, -3]; 6 mm), thalamus ([±12, -18, 3]; 6 mm), and periaqueductal gray ([0, -32, -10]; 6 mm). Importantly, to pass this second check, we did not expect all investigated regions to be modulated by the placebo induction and task, as our design was not equivalent to previously used designs.

Third, to check that the design evoked empathic responses that overlapped with the first-hand experience of pain, we performed a conjunction analysis between self- and other-related conditions using the contrast *[self - pain > self - no pain]* ∩ *[other - pain > other - no pain]* for the control hand only (manipulation check b3 in Figure 2). We chose this analysis approach in line with the meta- analysis by Lamm et al. (2011) and the original approach proposed by Singer et al. (2004). However, this preregistered check did not reveal any significant clusters, when using a whole brain and FWE-cluster-corrected approach. The following checks were therefore added post hoc: To investigate this overlap in previously reported affective brain regions related to empathy, we adopted a SVC approach on three ROIs from an independent meta-analysis using the above two contrasts (Lamm et al., 2011): left AI [-40, 22, 0], right AI [39, 23, -4] and aMCC [-2, 23, 40] (all 10 mm), again $p < .05$ FWE-corrected at peak-level. Furthermore, to maximize sensitivity and detect any overlap between self- and empathy-related conditions, we additionally reported the same conjunction with contrasts averaging over both hands. In this third check we expected especially aMCC and AI to overlap for self- and other-related stimulation in order to pass it.

Preregistered analyses. Our first aim was to replicate our previous study (Rütgen, Seidel, Silani, et al., 2015) of a transfer of first-hand placebo analgesia to empathy for pain in brain regions involved in affective processing (i.e., aMCC and AI) using our adapted paradigm. In a second step, we aimed to test our hypothesis of a somatosensory-specific transfer of this effect to empathy for pain. To this end, we conducted ROI analyses in bilateral AI and aMCC

(see coordinates above taken from Lamm et al., 2011), as well as in bilateral S1 and S2 (left S1: [-39, -30, 51]; right S1: [36, -36, 48]; left S2: [-39, -15, 18]; right S2 [39, -15, 18]; see Figure 3). S1/S2 coordinates were taken from independent findings investigating first-hand somatosensory pain perception (Bingel et al., 2004 for S1, Bingel et al., 2007 for S2). We created 10 mm spheres around each coordinate with MarsBaR (Brett et al., 2002) and then extracted parameter estimates for each ROI from the first-level contrast images of each participant and for each condition using REX (Duff et al., 2007). The specific coordinates and sphere sizes for the ROI analyses were not preregistered, but we again adhered to procedures used in Rütgen, Seidel, Silani, et al. (2015).

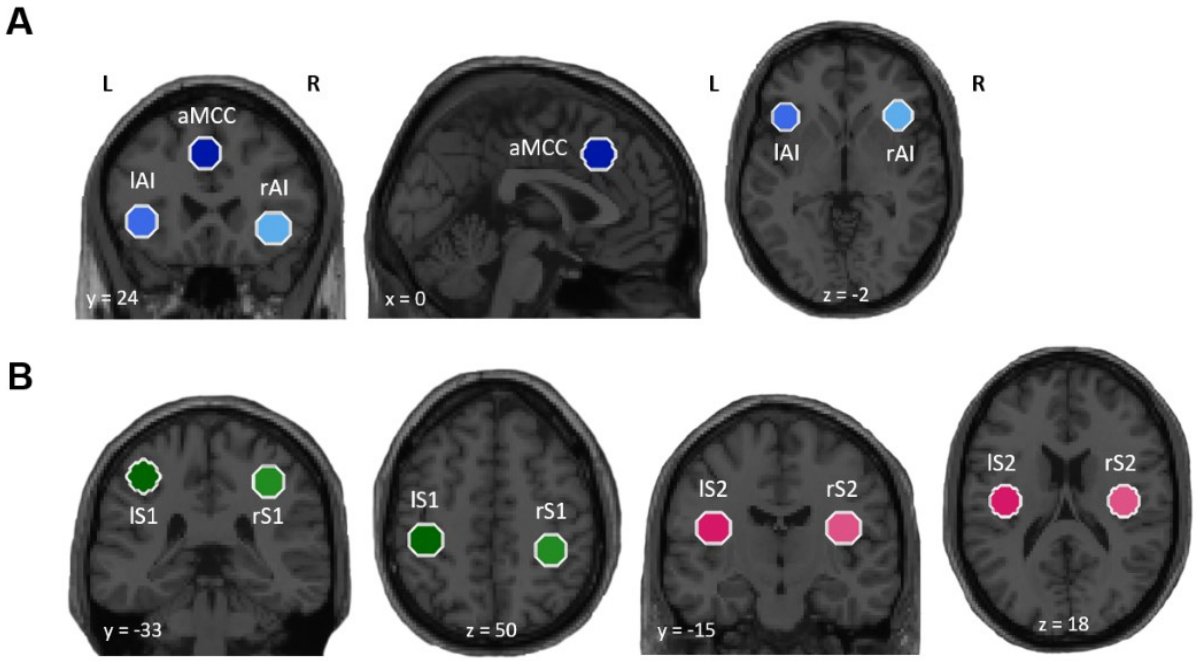


Figure 3. Overview of the seven regions of interest (ROIs) used in the main analysis. We analysed the transfer of the first-hand placebo effect to empathy for pain in A) three affective and B) four somatosensory brain regions (all 10 mm spheres; MNI coordinates [x, y, z]: left/right anterior insula (lAI: [-40, 22, 0]; rAI: [39, 23, -4]), anterior midcingulate cortex (aMCC: [-2, 23, 40]), left/right primary somatosensory cortex (lS1: [-39, -30, 51]; rS1: [36, -36, 48]; left/right secondary somatosensory cortex (lS2: [-39, -15, 18]; rS2: [39, -15, 18]; anatomical brain regions were confirmed with the SPM Anatomy toolbox version 2.15 by Eickhoff et al., 2005). Bilateral AI and aMCC coordinates were taken from an independent meta-analysis on networks involved in (empathic) pain (Lamm et al., 2011), while bilateral S1/S2 coordinates were taken from two studies investigating somatosensory pain perception (Bingel et al., 2004 for S1, Bingel et al., 2007 for S2). L = left hemisphere, R = right hemisphere. Figure taken from Hartmann, Rütgen, Riva, et al. (2021).

ROI analyses were conducted in RStudio Version 3.6.1 (R Core Team, 2020). Mimicking the behavioral analysis, we implemented the same within-subjects, full-factorial design with

three factors (*treatment*, *target*, *intensity*) of two levels each, and the additional factor *ROI* with seven levels (pooled activation of lAI, rAI, aMCC, lS1, rS1, lS2, and rS2; analysis B1 in Figure 2).

In the pooled ANOVA, Mauchly's test for sphericity was significant for the main effect of ROI and all interactions with the factor ROI, which is why those results are reported using Greenhouse Geisser sphericity correction. Due to the significant main effect of ROI and interactions with the factor ROI in the initial four-way ANOVA, we proceeded with our preregistered analysis plan by computing separate ANOVAs and planned comparisons for each of the ROIs (analysis B2 in Figure 2). Again, all preregistered *t*-tests were conducted one-tailed. As we tested the same hypotheses in three affective and four somatosensory ROIs, we corrected for multiple comparisons using Bonferroni correction and dividing the *p*-value by the number of ROIs separately for affective- and somatosensory-related tests (for tests in affective ROIs: $p = .05 / 3$ ROIs $= .017$; somatosensory ROIs: $p = .05 / 4$ ROIs $= .013$).

Post hoc analyses. Again, we aimed to gather further relative evidence for the null vs. the alternative hypothesis, using a Bayesian approach and calculated one paired *t*-test per ROI mirroring the preregistered analyses, adding up to seven additional tests. Mirroring the behavioral Bayesian analyses, we used a standard Cauchy (0,1) prior of 1 as the effect size. Those results can be found in Table 15 in Supplement A (see also analysis B4 in Figure 2).

Our preregistered main analysis tested for the difference between placebo and control hand in each ROI, e.g., activation differences in right S1 during stimulation of left (contralateral) control hand vs. right (ipsilateral) placebo hand. However, although stimulation of one body site often evokes bilateral activation, most studies investigating somatosensation of noxious and non-noxious stimuli report a strong contralateral bias, i.e. a location coding in the contralateral hemisphere for S1 and S2 (Bingel et al., 2003, 2004; Ogino et al., 2005; Tamè et al., 2012; Wager et al., 2004). Thus, our preregistered analysis

approach was not optimized to deal with possible laterality issues in these two regions. Therefore, to gather additional evidence that our participants had in fact a first-hand placebo analgesia effect that was localized, or in other words, specific for the right hand (and to ensure that this effect did in fact not transfer to empathy), we conducted a hemispheric comparison (analysis B3 in Figure 2). This analysis was aimed at directly comparing activation in each hemisphere but focusing on activation only related to stimulation of the contralateral hand, by "cleaning" the signal of activation related to the other hand in the same areas. As the ipsilateral hand served as the "control condition" in the present paradigm, we were interested only in specific somatosensory activity related to the contralateral hand via subtracting the unspecific baseline activation that generally occurs in response to somatosensory stimulation, irrespective of the targeted hand. This way, we wanted to contrast any activation in the left hemisphere related to the right placebo hand with the activation in the right hemisphere related to the left control hand. We focused this analysis on S1 and S2, since both have been found to provide spatial information of painful and non-painful stimulation in the hemisphere contralateral to the stimulated body side (Bingel et al., 2003). However, while S1 is more often reported in relation to general stimulation (Keysers et al., 2004; Ploner et al., 2000), S2 additionally seems to encode stimulus intensity and play a greater role in the processing of pain (Lockwood et al., 2013). Furthermore, involvement of S2 in placebo analgesia mechanisms has been reported, making S2 an especially optimal candidate for testing the localized first-hand placebo analgesia effect in our study (Bingel et al., 2003, 2004, 2007; Eippert et al., 2009; Geuter et al., 2013; Price et al, 2007; Schenk et al., 2014; Wager et al., 2011, 2004). To this end, we used the previously extracted parameter estimates of left and right S1 and S2. Mirroring previous approaches, we used the pain conditions only (e.g. Eippert et al., 2009; Rütgen, Seidel, Silani, et al., 2015; Zubieta et al., 2005). For each region and hemisphere, we subtracted activation related to the ipsilateral

hand from activation related to the contralateral hand, leaving us with the following contrasts: lS1 (right placebo hand - left control hand), rS1 (left control hand - right placebo hand), lS2 (right placebo hand - left control hand) and rS2 (left control hand - right placebo hand). Then, we used these resulting values to compare activation in left S1 (now related only to the right placebo hand) with activation in right S1 (now related only to the left control hand) and the same for S2 via two-tailed paired *t*-tests. This was done separately for self- and other-related stimulation.

3.2.5 Results

Behavioral results

The two manipulation checks showed a strong belief in the effectiveness of the placebo gel over the course of the session and a robust behavioral placebo effect even afterwards (manipulation checks a1 and a2 in Figure 2; see A.6 and Figure Figure *9* in Supplement A).

Preregistered analyses. To evaluate the existence of a localized first-hand placebo analgesia effect for pain as well as the transfer of this effect to other-related pain and self-experienced unpleasantness, we calculated two repeated-measures ANOVAs. The first ANOVA using self- and other-related pain ratings revealed all main effects and interactions to be significant (analysis A1 in Figure 2; see Table 2 in Supplement A and Figure 4 for an overview of all behavioral ratings). Planned comparisons showed a significant placebo analgesia response for self-related but no transfer to other-related stimulation (self: $t(44) = 9.49$, $p < .001$ one-tailed, $M_{diff} = 1.619$, 95% $CI_{meandiff}$ [1.28, 1.96], Cohen's $d_z = 1.42$; other: $t(44) = -0.17$, $p = .435$ one-tailed, $M_{diff} = 0.018$, 95% $CI_{meandiff}$ [-0.23, 0.19], Cohen's $d_z = 0.03$). Indeed, the mean ratings were decreased in the placebo compared to the control hand for first-hand stimulation (see Figure 4). This was not the case for pain empathy, where the mean ratings for the two hands were similar. The magnitude of the placebo effect, i.e., the difference between placebo and control hand, was significantly higher in the self, compared

to the other (self vs. other: $t(44) = -8.22$, $p < .001$ one-tailed, $M_{diff} = -1.64$, 95% $CI_{meandiff}$ [-2.04, -1.24], Cohen's $d_z = 1.23$).

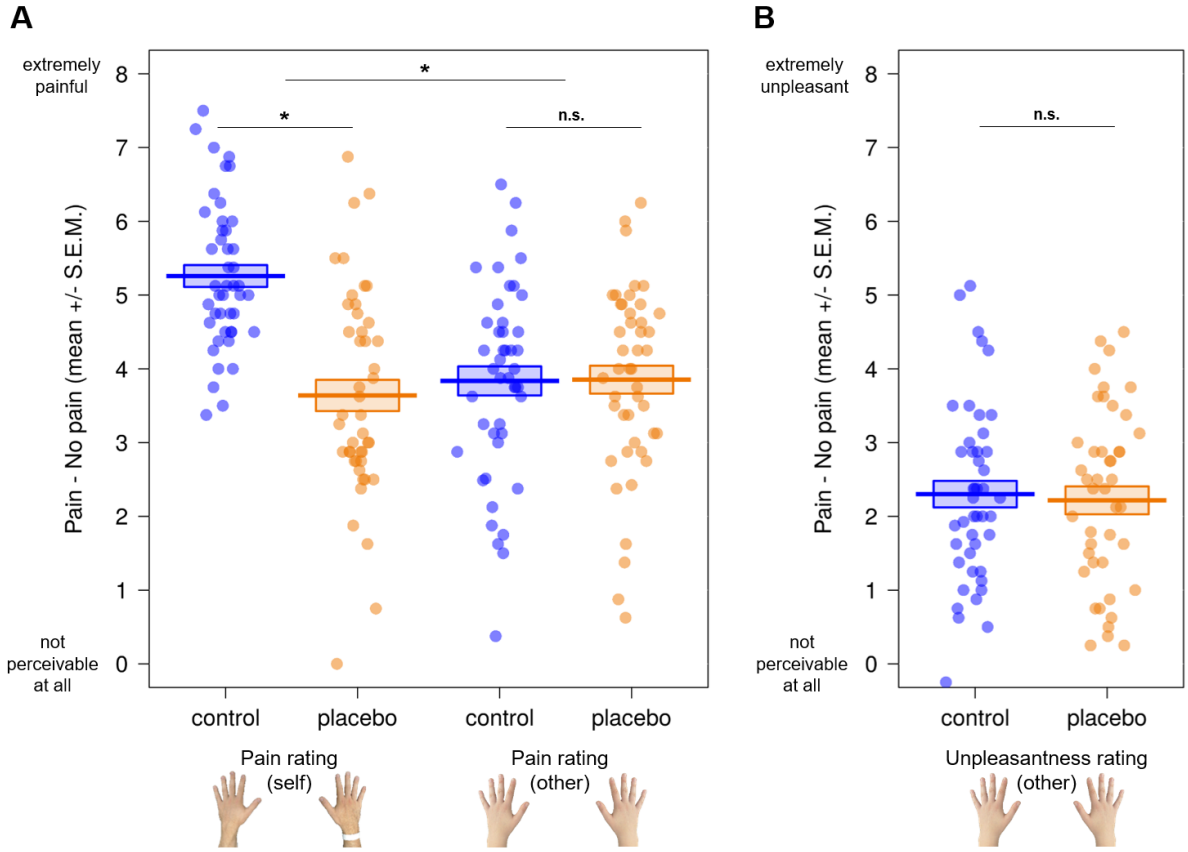


Figure 4. Behavioral results of the pain task. Participants rated electrical stimulation they either received themselves or witnessed another person receiving (displayed here as an index of the ratings for pain - no pain conditions). Using paired *t*-tests, we observed a significant placebo effect for self-related pain ratings, but no transfer to other-related pain (A) or other-related unpleasantness ratings (B) when observing the other in pain. * $p < .05$; n.s. = not significant; S.E.M. = standard error of the mean. Figure taken from Hartmann, Rütgen, Riva, et al. (2021).

The second ANOVA, using ratings of the participants' own unpleasantness while watching the confederate receiving stimulation, showed similar results, with a main effect of intensity but no hand x intensity interaction (analysis A2 in Figure 2; see Table 3 in Supplement A). The planned comparison indicated no placebo analgesia effect related to one's own unpleasantness ($t(44) = 0.69$, $p = .245$ one-tailed, $M_{diff} = 0.084$, 95% $CI_{meandiff}$ [-0.16, 0.33], Cohen's $d_z = 0.10$). Participants experienced a similar amount of unpleasant affect when witnessing the other's pain on either hand. In other words, there was no transfer

of the first-hand placebo analgesia effect, neither to empathy for pain nor to one's own unpleasantness.

Post hoc analyses. Complementing the above results, the Bayesian paired t-tests using self- and other-related pain as well as unpleasantness ratings showed very strong evidence for a placebo analgesia effect in first-hand pain (BF10 = 3.15 × 109), but strong evidence against such an effect in pain empathy (analysis A3 in Figure 2). The latter was visible in the other-related pain ratings where the null hypothesis was found to be approximately eight times more likely than the alternative hypothesis in our sample (BF_{01} = 8.47). For unpleasantness ratings, the null hypothesis was found to be approximately seven times more likely than the alternative hypothesis (BF_{01} = 6.80). In sum, the behavioral results suggested a strong placebo analgesia effect for self-related pain, localized to participants' right hands, but no transfer of this effect to other-related pain or self-experienced unpleasantness.

fMRI results

Manipulation checks. We preregistered three manipulation checks to evaluate the (i) validity of our design, (ii) success of the first-hand placebo analgesia induction and (iii) existence of overlapping activation for self- and other-related pain (see Figure 5).

For check (i), the contrast *[self - pain > self - no pain]* for the control hand revealed increased hemodynamic activity in three major clusters encompassing, among others, ACC, MCC, bilateral insula, bilateral S2, thalamus and cerebellum (manipulation check b1 in Figure 2; see A.7 and Table 4 in Supplement A) whole brain, $p < .05$ FWE-corrected at cluster level). Having verified the overall validity and effectiveness that typical sensory-discriminative and affective-motivational areas of first-hand pain processing were activated by our task, making check (i) successful.

For check (ii), we evaluated the contrasts [*self - pain - control hand > self - pain - placebo hand]* and [*self - pain - placebo hand > self - pain - control hand]* (manipulation check b2 in

Figure 2; see A.7 and Table 5 in Supplement A; SVC, $p < .05$ FWE-corrected at peak-level). We found increased hemodynamic activity in right S2, right posterior insula, bilateral dACC, bilateral AI and thalamus when participants received painful stimulation on the left control compared to the right placebo hand. In the opposite contrast, we observed increased activity in right DLPFC and left S2 for the right placebo compared to the left control hand.

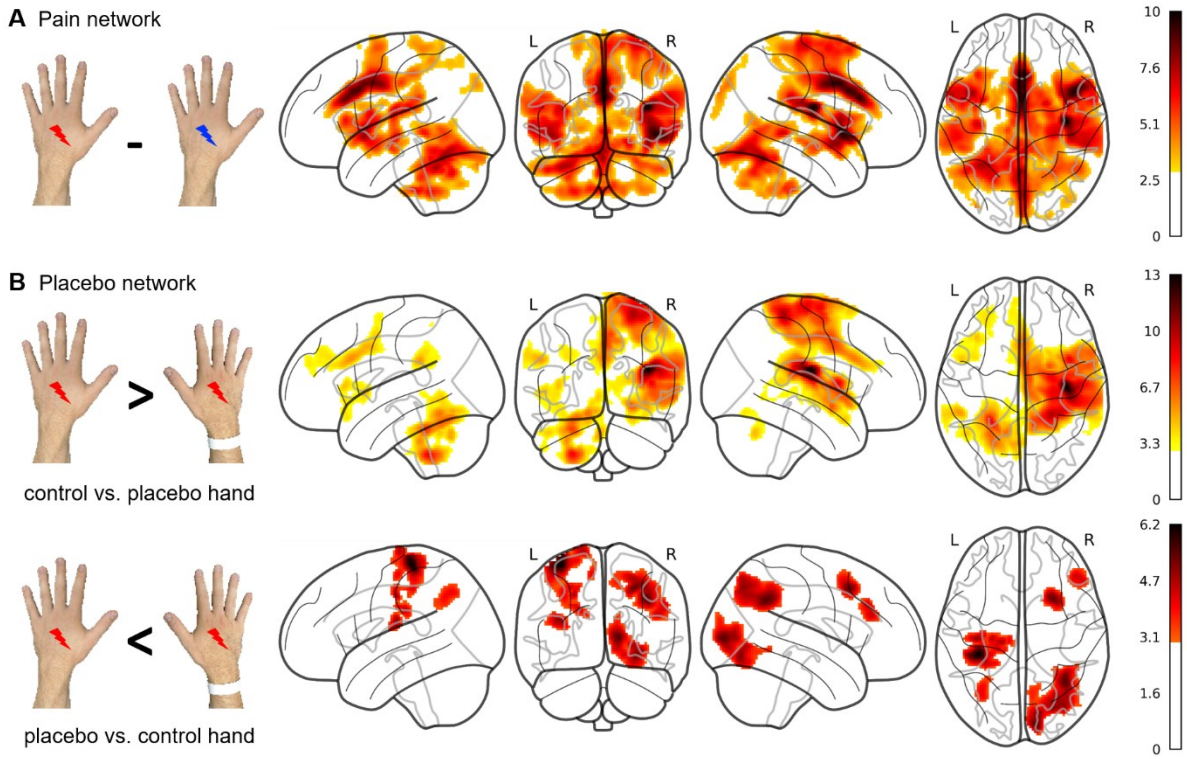


Figure 5. Preregistered manipulation checks of the fMRI data (see also Figure 2). A) Check b1 aimed at showing the first-hand pain processing network induced by electrical stimulation and is displayed as the contrast [*self - pain* (red icon) > *self - no pain* (blue icon)] for the control hand only. Here, we observed increased activity in both affective-motivational and sensory-discriminative pain processing regions. B) Check b2 aimed at evaluating the existence of a placebo analgesia network and is displayed using the contrasts *[self - pain - control hand > self - pain - placebo hand]* and *[self - pain - placebo hand > self - pain - control hand]* (results of this check are reported in the text using small volume correction (SVC) on specific regions). There, we observed the typical placebo network and initial evidence for a first-hand localized placebo effect. Check b3 was done using SVC and is therefore not displayed in here but used the conjunction *[self - pain > self - no pain]* ∩ *[other - pain > other - no pain]*. This revealed increased activation in left AI when using only the control hand, and bilateral AI as well as aMCC when averaging over both hands. All statistical activation maps in the figure are displayed whole brain, FWE-corrected at $p < .05$ cluster correction ($k = 188$) and an initial cluster-forming threshold of $p < .001$ uncorrected. L = left hemisphere; R = right hemisphere. Figure taken from Hartmann, Rütgen, Riva, et al. (2021).

As whole brain results of these two contrasts encompassed multiple additional regions, these results are reported in Table 6 in Supplement A. Due to these results showing the

typical placebo analgesia network to a sufficient degree (although, as in our previous publication, not all regions investigated were found), we considered check (ii) sufficiently passed as well.

For check (iii), the conjunction *[(self pain > self no pain) ∩ (other pain > other no pain)]* using contrasts of the control hand revealed increased activation in left AI (manipulation check b3 in Figure 2; SVC, $p < .05$ FWE-corrected at peak-level). When averaging over both hands, we observed increased hemodynamic activity in bilateral AI and aMCC. Although this (iii) check did not result in the expected activation when using the same threshold as in our previous study, we did find an overlap when restricting the analysis to our a-priori specified ROIs. We thus considered this enough evidence to continue with the main analyses.

Preregistered analyses. After having verified the overall validity and effectiveness of the experimental paradigm as well as the placebo induction procedures to a sufficient degree, we went on to test our main hypothesis for a transfer of the first-hand placebo analgesia effect to empathy for pain using a ROI approach (see Table 1 for an overview of all paired *t*-tests). To this end, we extracted parameter estimates of three affective (bilateral AI, aMCC) and four somatosensory ROIs (bilateral S1 and S2). We first calculated an ANOVA pooling the activation of all seven ROIs and then calculated separate ANOVAs and planned comparisons for each ROI to evaluate the first-hand placebo effect, its transfer to pain empathy, and to compare the effects for self- and other-related stimulation. The pooled ANOVA (analysis B1 in Figure 2) showed significant main effects of target, hand, intensity and ROI, a significant target x intensity interaction, as well as all interactions involving the factor ROI (except for the four way interaction target x hand x intensity x ROI, see Table 7 in Supplement A). When comparing brain activity related to the placebo vs. the control hand encompassing pooled activation of all ROIs, we found no significant differences for self-related or other-related stimulation (self: $M_{diff} = 0.212$, 95% $CI_{meandiff}$ [-0.44, 0.86]; other: $M_{diff} = 0.072$, 95% $CI_{meandiff}$

[-0.55, 0.70]). The magnitudes of these effects were indistinguishable between self and other (self vs. other: M_{diff} = -0.139, 95% $CI_{meandiff}$ [-1.18, 0.90]). The absence of effects in the pooled ANOVA might be explained by differential, inhomogeneous effects in the seven ROIs. As preregistered, and due to a significant main effect of ROI as well as significant interactions with the factor ROI, we went on to calculate single ANOVAs and complementary *t*-tests for each ROI separately (analysis B2 in Figure 2).

Table 1

Main ROI analyses testing for self- and other-related placebo effects in affective and somatosensory brain regions, as well as for differences between self- and other-related effects via paired t-tests.

		self			**other**			**self vs. other**		
		t(44)	*p*	d_z	*t*(44)	*p*	d_z	*t*(44)	*p*	d_z
B1	pooled ROIs	0.66	.256	0.09	0.23	.409	0.03	-0.27	.394	-0.04
B2	left AI	1.60	**.059^t**	0.24	0.67	.254	0.10	-0.63	.267	0.09
	right AI	0.41	.341	0.06	-0.54	.298	0.08	-0.57	.285	0.09
	aMCC	-0.07	.473	0.01	0.41	.341	0.06	0.32	.376	0.05
	left S1	-0.20	.423	0.03	0.42	.338	0.06	0.39	.349	0.06
	right S1	0.28	.391	0.04	0.35	.366	0.05	0.04	.483	0.006
	left S2	-1.87	**.034^t**	0.28	-0.95	.174	0.14	0.57	.285	0.09
	right S2	3.27	**.001***	0.49	0.37	.355	0.06	-1.87	**.034^t**	0.28
B3	lS1 vs. rS1	0.88	.385	0.13	-0.74	.465	0.11	1.07	.292	0.16
	lS2 vs. rS2	-4.30	**<.001***	0.64	-0.75	.455	0.11	-2.85	**.006***	0.42

Note. Planned comparisons for the region of interest (ROI) analyses (analyses B1 and B2 in Figure 2) to evaluate the first-hand placebo effect (self), its transfer to pain empathy (other) and to compare the effects for self- and other-related stimulation (self vs. other). Furthermore, analysis B3 (here and in Figure 2) directly compared activity in right vs. left S1, and right vs. left S2, related only to stimulation of the contralateral hand. *p* values for preregistered analyses B1 and B2 are reported one-tailed, and Bonferroni corrected for multiple comparisons (p = .017 for affective ROIs and p = .013 for somatosensory ROIs), and two-tailed for analysis B3. AI = anterior insula; aMCC = anterior midcingulate cortex; r/lS1 = right/left primary somatosensory cortex; r/l S2 = right/left secondary somatosensory cortex; *t*(degrees of freedom); d_z = Cohen's *d*; ^{t} = trend; * $p < .05$.

The separate ROI analyses of the three affective regions revealed a trend in left AI for self- but not for other-related stimulation, with the control hand showing slightly increased activation compared to the placebo hand (self: M_{diff} = 0.825, 95% $CI_{meandiff}$ [-0.22, 1.87]; other: M_{diff} = 0.315, 95% $CI_{meandiff}$ [-0.63, 1.26]). We found no significant differences between placebo and control hand in right AI or aMCC, neither for self- nor other-related

stimulation (right AI, self: M_{diff} = 0.200, 95% $CI_{meandiff}$ [-0.78, 1.18], other: M_{diff} = 0.211, 95% $CI_{meandiff}$ [-1.00, 0.58]; aMCC, self: M_{diff} = 0.034, 95% $CI_{meandiff}$ [-1.04, 0.97], other: M_{diff} = 0.218, 95% $CI_{meandiff}$ [-0.85, 1.29]). The magnitudes of these effects were indistinguishable between self and other (self vs. other, left AI: M_{diff} = -0.510, 95% $CI_{meandiff}$ [-2.15, 1.13]; right AI: M_{diff} = -0.411, 95% $CI_{meandiff}$ [-1.86, 1.04]; aMCC: M_{diff} = 0.253, 95% $CI_{meandiff}$ [-1.35, 1.86]; see Figure 6 here and Tables 8 - Table *10* in the Supplement).

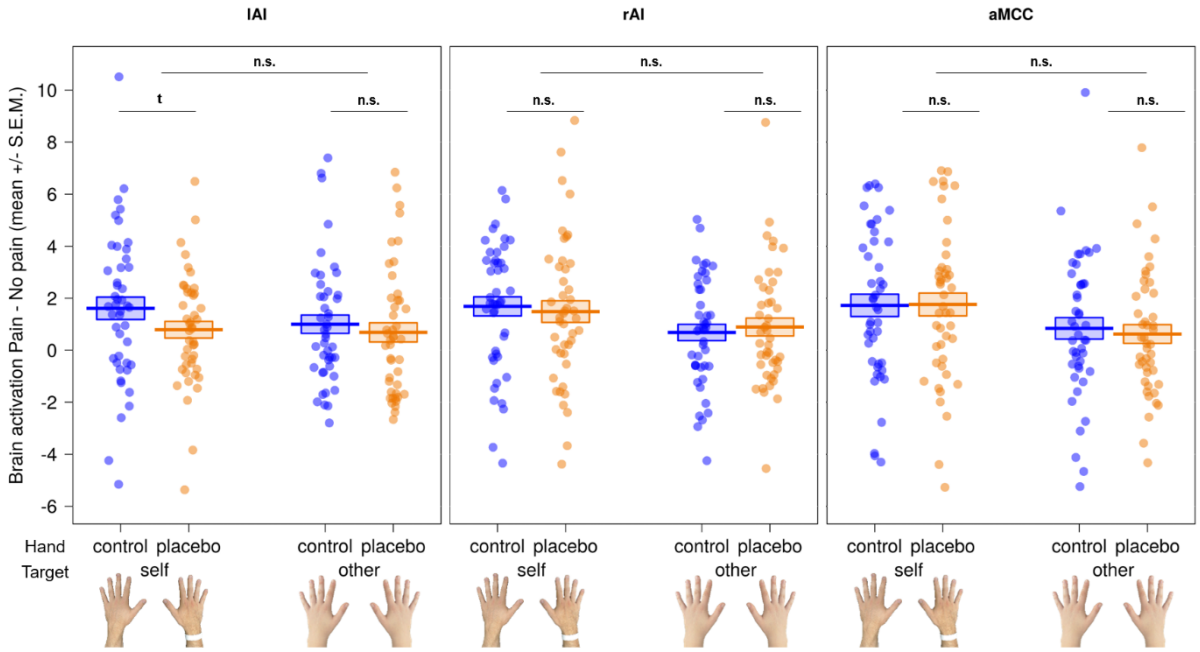
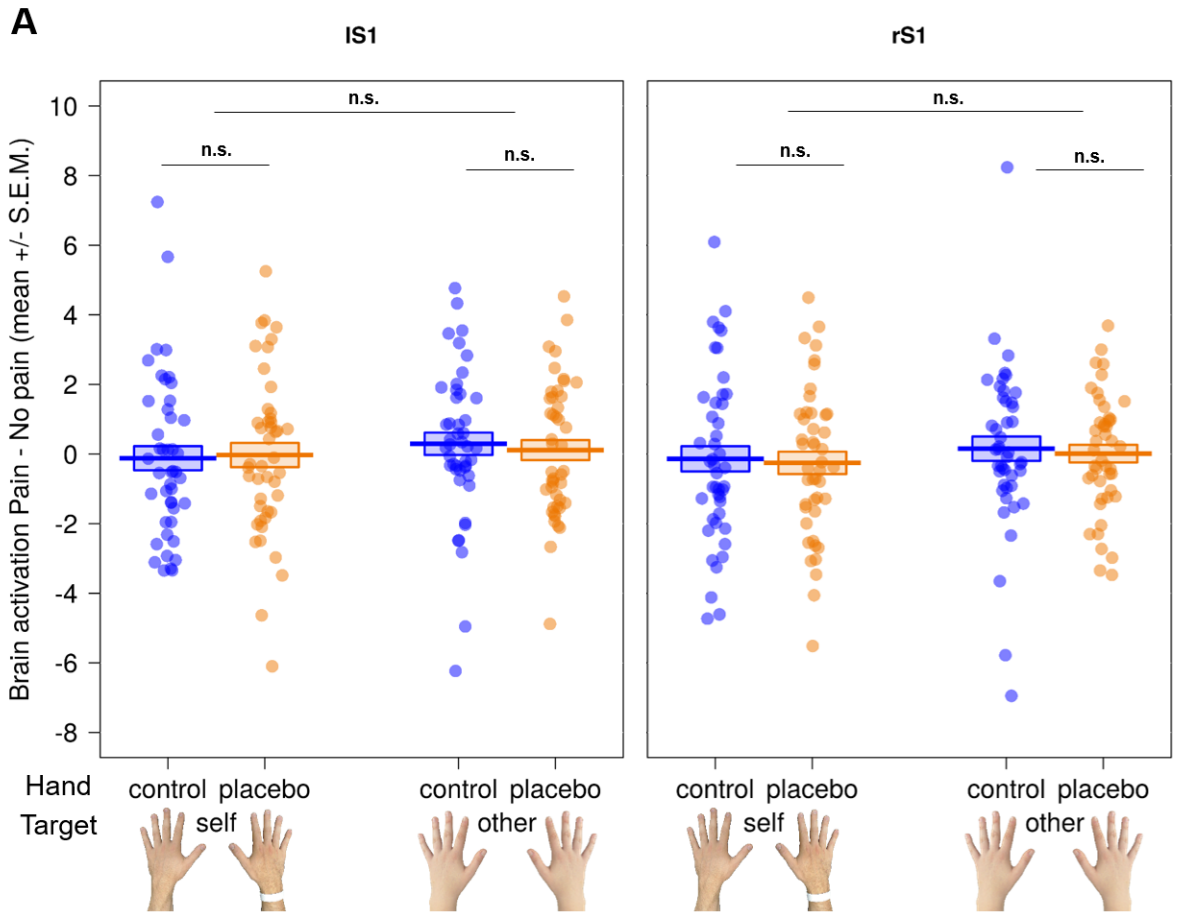


Figure 6. Paired comparisons of the region of interest (ROI) results for affective brain regions. Results in left anterior insula (lAI), right anterior insula (rAI) and anterior midcingulate cortex (aMCC) revealed no modulation in the three affective ROIs for self or other by the placebo manipulation. In other words, both hands led to similar hemodynamic activity in each ROI. We did find a trend (*t*) of p = .059 one-tailed in left AI, with increased activity during stimulation of the control hand in the self condition. n.s. = not significant; S.E.M. = standard error of the mean. Figure taken from Hartmann, Rütgen, Riva, et al. (2021).

The four somatosensory ROIs showed differential results for S1 and S2. The planned comparisons in S1 revealed no differences between the hands, neither for self- nor other-related stimulation (left S1, self: M_{diff} = -0.091, 95% $CI_{meandiff}$ -1.03, 0.85], other: M_{diff} = 0.181, 95% $CI_{meandiff}$ [-0.68, 1.04]; right S1: self: M_{diff} = 0.116, 95% $CI_{meandiff}$ [-0.73, 0.96], other: M_{diff} = -0.142, 95% $CI_{meandiff}$ [-0.69, 0.97]). The magnitudes of these effects were indistinguishable between self and other (self vs. other, left S1: M_{diff} = 0.271, 95% $CI_{meandiff}$ [-1.13, 1.67]; right S1: M_{diff} = 0.026, 95% $CI_{meandiff}$ [-1.22, 1.27]).

For right S2, however, we observed significant differences between placebo and control hand for self- but not for other-related stimulation (self: M_{diff} = 0.928, 95% $CI_{meandiff}$ [0.36, 1.50]; other: M_{diff} = 0.124, 95% $CI_{meandiff}$ [-0.54, 0.79]), while left S2 only showed a trend using a Bonferroni-corrected α = .013 (self: M_{diff} = -0.461, 95% $CI_{meandiff}$ [-0.96, 0.04], other: M_{diff} = -0.262, 95% $CI_{meandiff}$ [-0.82, 0.30]). Interestingly, activity in left S2 was higher for the contralateral placebo hand while this effect was reversed in right S2 (higher activity for contralateral control hand; see panel A in Figure 7 here and Tables Table *11* and Table *12* in Supplement A for full ANOVAs). The magnitudes of these effects were not different between self and other in left S2, but we found a trend in right S2, where the difference between the two hands was higher for the self condition (self vs. other, left S2: M_{diff} = 0.199, 95% $CI_{meandiff}$ [-0.50, 0.90]; right S2: M_{diff} = -0.804, 95% $CI_{meandiff}$ [-1.67, 0.06]; see panel B in Figure 7 here and Tables Table *13*Table 14 in Supplement A for full ANOVAs).



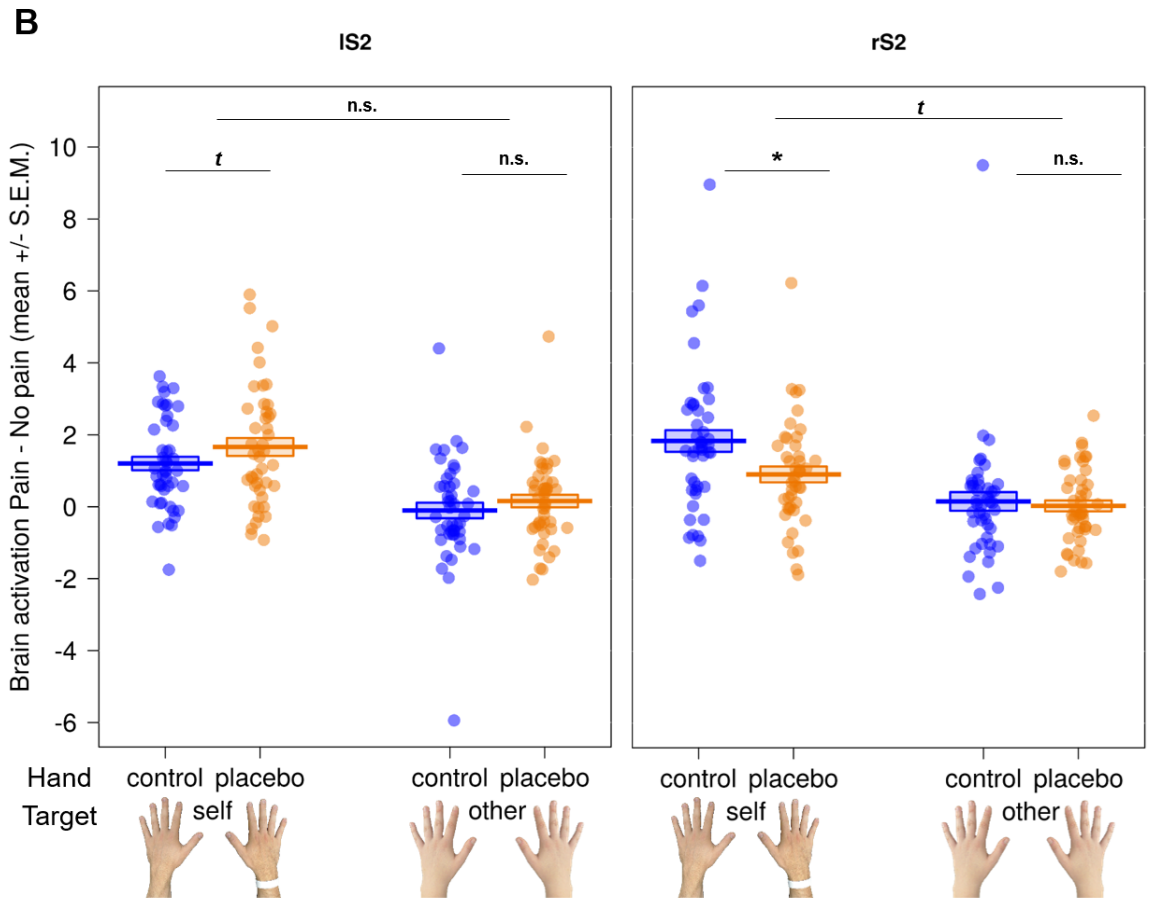


Figure 7. Paired comparisons of the region of interest (ROI) results for somatosensory brain regions. A) Results in left (lS1) and right (rS1) primary somatosensory cortex revealed no evidence for a modulation by the placebo manipulation in either hemisphere, neither for self nor other. B) Results in left (lS2) and right (rS2) secondary somatosensory cortex showed differential effects: In the self condition, hemodynamic activity was significantly higher in rS2 for the contralateral control hand. Generally, we found no significant differences regarding other-related stimulation, but a trend that the first-hand placebo effect in lS2 was significantly stronger than its other-related counterpart. *p < .013 (Bonferroni-corrected for multiple comparisons); n.s. = not significant; t = trend; S.E.M. = standard error of the mean. Figure taken from Hartmann, Rütgen, Riva, et al. (2021).

Post hoc analyses. The Bayesian *t*-tests Lastly, to gather more evidence for a localized placebo effect, we compared activation in each hemisphere related only to the contralateral hand with each other, for self- and other-related stimulation, respectively (analysis B3 in Figure 2; see Table 1 and Figure 8). Mirroring the ROI results above, we found differential results for S1 and S2. Regarding S1, there was no difference in brain activation between control and placebo hand for self- or other-related stimulation (self: M_{diff} = 0.553, 95% $CI_{meandiff}$ [-0.72, 1.82]; other: M_{diff} = -0.37, 95% $CI_{meandiff}$ [-1.37, 0.64]). The magnitude of

these effects did not differ between self and other (self vs. other: M_{diff} = 0.92, 95% $CI_{meandiff}$ [-0.82, 2.66]).

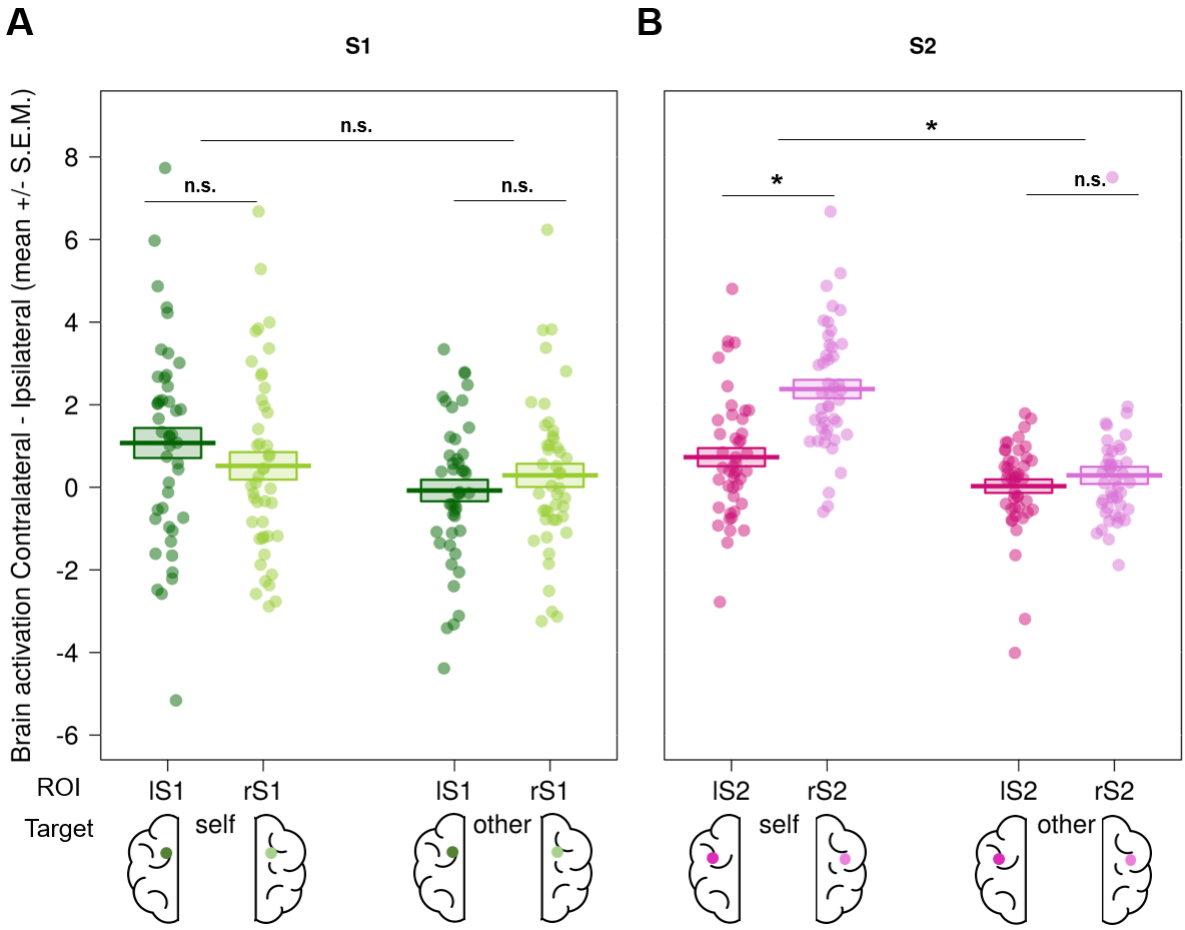


Figure 8. Evidence for a first-hand localized placebo analgesia effect in secondary somatosensory cortex (S2). We compared activity for each hemisphere related only to the contralateral hand with each other, i.e., activation in right primary somatosensory cortex (S1) during stimulation of left (contralateral) control hand vs. activation in left S1 during stimulation of the right (contralateral) placebo hand, and the same for secondary somatosensory cortex (S2). This was done separately for self- and other-related stimulation. A) For S1, we found no evidence for a modulation by the placebo manipulation. B) For S2, we observed increased activity in right compared to left S2 in the self condition. In general, we did not find a difference between hemispheres for the other-condition. The difference in S2 for first-hand pain was significantly stronger than its other-related counterpart. *p < .05; n.s. = not significant; S.E.M. = standard error of the mean. Figure taken from Hartmann, Rütgen, Riva, et al. (2021).

Regarding S2, we found a significant difference in brain activation between control and placebo hand for self-related pain, with the right S2 contralateral to the control hand showing increased activation compared to the left S2 contralateral to placebo hand (rS2 vs. lS2 for self: M_{diff} = -1.65, 95% $CI_{meandiff}$ [-2.42, -0.88]); $M_{rS2} \pm SD$ = 2.38 ± 1.49, $M_{lS2} \pm SD$ = 0.73 ± 1.48). In other words, stimulation of the control hand produced significantly greater

contralateral S2 activation than stimulation of the placebo hand. Regarding other-related stimulation, we did not find a difference between the right and left S2 (rS2 vs. lS2 for other: M_{diff} = -0.26, 95% $CI_{meandiff}$ [-0.96, 0.44]; $M_{rS2} \pm SD$ = 0.29 ± 1.39, $M_{lS2} \pm SD$ = 0.03 ± 1.09). Comparing these two effects between self and other showed a significant difference, i.e., evidence for a placebo effect for the self, but not for the other (self vs. other: M_{diff} = -1.39, 95% $CI_{meandiff}$ [-2.37, -0.41], $M_{self} \pm SD$ = 1.65 ± 2.57, $M_{other} \pm SD$ = 0.26 ± 2.32).

In sum, we replicated previous results regarding shared activations, as we observed an overlap of affective brain regions for self- and other-related stimulation. In line with the behavioral results, the fMRI results suggested that we successfully induced a localized first-hand placebo analgesia effect in the right hand of our participants, visible in increased brain activity related to the left control hand in contralateral S2. This effect, however, did not transfer to empathy for another's pain, as we did not observe modulation of brain activity in S2 (or S1) by the placebo in the empathy condition.

3.2.6 Discussion

In this preregistered study, we addressed the debated question concerning the role that somatosensory aspects of the first-hand pain experience play during empathizing with someone else in pain. In particular, we wanted to pinpoint whether, when we witness another's pain, sharing their somatosensory representations plays a similar causal role as previously shown for affective representations (e.g. Rütgen, Seidel, Silani, et al., 2015). To test this question, we induced localized placebo analgesia on the right hand of 45 participants by means of a placebo gel (with the left hand acting as a control). We then measured brain activity with fMRI during a pain task tailored towards observing possible involvement of the sensory-discriminative component of empathic pain processing. While our findings indicated both behavioral and fMRI evidence for a robust first-hand, localized placebo analgesia effect, we did not observe a transfer of this effect to empathy for pain. We thus found no causal

evidence for the involvement of the sensory-discriminative component in the processing of empathic pain.

Regarding pain empathy, our findings replicated the well-documented overlap between first-hand and empathy for pain in bilateral AI and aMCC, as reported extensively in previous studies (Corradi-Dell'Acqua et al., 2011; Lamm et al., 2011 for a meta-analysis; Ochsner et al., 2008; Singer et al., 2004; Zaki et al., 2016 for a review). Importantly, these results emerged only when restricting the analysis to our a-priori specified ROIs using SVC and were more pronounced when averaging over both control and placebo hand compared to only using the control hand. Moreover, the other-related pain and self-experienced unpleasantness ratings indicated that participants engaged in the task and felt empathy for the other person. Thus, participants not only correctly evaluated the pain of the other person, but also showed an empathic response. However, despite these findings, we did not observe a localized transfer of the first-hand placebo analgesia effect to empathy. Behaviorally, participants showed no reduction in empathy ratings for the placebo hand. This lack of inference-statistical significance was further corroborated by much smaller effect sizes, and strong evidence against a transfer of this effect to empathy in the Bayesian analyses. Analysis of the fMRI data directly mirrored these results, as we did not observe any differences in other-related brain activation between the two hands.

Although we did not observe a transfer of the placebo analgesia effect to empathy for pain, our behavioral results regarding self pain showed a strong, localized placebo analgesia effect, as evidenced by significantly reduced pain ratings for the placebo hand compared to the control hand, a large effect size and very strong evidence for this effect in the Bayesian analyses. This was expected, as our sample criteria excluded nonresponders to the placebo manipulation. We corroborated this finding on the neural level by showing increased activation in right S2 during stimulation of the contralateral control hand compared to the

placebo hand, while this effect was reversed in left S2, which indicated stronger activation for the contralateral placebo hand (although the latter was only a trend after Bonferroni-correction). These results mirror studies finding a contralateral bias in somatosensory brain areas (Bingel et al., 2003; Coghill et al., 1999; Ploner et al., 1999; Singer et al., 2004; Symonds et al., 2006). When specifically comparing contralateral activation related to each hand with each other, we found further evidence in S2, with stronger activation in right S2 (related to the contralateral control hand) compared to left S2 (related to the contralateral placebo hand). Furthermore, we observed increased hemodynamic activity in affective brain areas and contralateral S2 in the control hand compared to the placebo hand, as well as increased activity in DLPFC and contralateral S2 during stimulation of the placebo hand compared to the control hand. These results replicate the typical placebo analgesia network reported in prior studies using similar local (Eippert et al., 2009; Geuter et al., 2013; Schafer et al., 2015; Schenk et al., 2014; Tinnermann et al., 2017), or global placebo analgesia inductions (Mischkowski et al., 2016; Rütgen, Seidel, Riečanský, et al., 2015; Rütgen, Seidel, Silani, et al., 2015; see Colloca et al., 2013; Meissner et al., 2011; Wager et al., 2011 for reviews). Together, these results demonstrate the successful induction of a first-hand, localized placebo analgesia effect on the behavioral and neural level (for S2). Interestingly, we found no evidence for such an effect in our chosen ROIs of right and left S1 representing the "hand areas". S1 has often been implicated in the processing of stimulation in general (Ploner et al., 2000) and our design subtracted non-painful stimulation to control for unspecific touch-related activation. In fact, we did not observe any activation in the whole brain contrast [*self - pain > self - no pain]* for both hands in the area we selected for our ROI analysis (Bingel et al., 2004), but instead observed activation in a different, more dorsomedial cluster.

Although we found increased brain activity in affective-motivational brain areas for the control compared to the placebo hand on a whole brain level, our ROI analyses did not show any modulation by the placebo manipulation during self-related stimulation (except for a trend in right AI showing increased activity for the control hand, consistent with our predictions). This may seem contradictory to what was reported by Rütgen, Seidel, Silani, et al. (2015). However, it should be noted that in that study, two groups with either placebo analgesia or control were compared, while the current design made comparisons within participants who all underwent placebo analgesia, with a specific focus on somatosensory aspects of the pain experience. Moreover, we employed a localized compared to a generalized placebo analgesia induction, which may also have influenced the affective-motivational component of first-hand pain. Thus, we cannot draw any conclusions about the here absent modulation of affective regions during self-experienced pain.

To answer our research question, we documented clear evidence for a localized placebo effect in first-hand pain but find no evidence for a transfer of this effect to empathy for pain, and thus no evidence for somatosensory sharing. As these results were contrary to our preregistered predictions, we now discuss why this could have been the case, highlighting strengths and possible limitations. First of all, we preregistered our design and procedure as well as most of the planned analyses prior to data collection and clearly distinguish those from post hoc analyses, thereby minimizing the possibility of false-positives and *p*-hacking (Crüwell, Stefan, et al., 2019; Nosek et al., 2018; Wicherts et al., 2016). Furthermore, we purposefully used a within-subjects design and an *a priori* power analysis to maximize sensitivity and the possibility of finding an effect (Beck, 2013; Charness et al., 2012). In contrast to previous studies, our design was specifically tailored to being able to observe possible somatosensory modulation. Our findings are further supported by observation of the typical pain processing network during first-hand electrical stimulation, demonstrating

validity of our pain paradigm (Morton et al., 2016; Xu et al., 2020). These points strongly speak for the validity of our design and additionally bolster the interpretability of our results.

Although we specifically targeted somatosensory pain processing, participants might still have focused more on the generalized, affective consequences of the other's pain instead of processing its localized, somatosensory consequences. This would be in line with results of an ERP study by Rütgen, Seidel, Riečanský, et al. (2015), who did not find effects of placebo analgesia on both anticipation and delivery phases in the ERP components P1 and N1 or on non-painful control stimulation (for both self- and other-related conditions). While P1 is an occipital ERP component that has been shown to index an early stage of low-level visual processing and was also linked to top-down attentional processes, the visual N1 component has been associated with attention and discrimination processes (Couperus & Mangun, 2010; Slagter et al., 2016). Due to these results, the authors argued that it is unlikely that placebo analgesia changed general aspects of sensory perception or attention in their study, but targeted affective aspects of the empathic pain experience. This might suggest that somatosensory-related processes are only or more strongly recruited by the first-hand pain experience and, therefore, do not play a strong role in empathic sharing (Decety, 2010; Jackson, Rainville, et al., 2006; Krishnan et al., 2016; Rütgen, Seidel, Riečanský, et al., 2015; Rütgen, Seidel, Silani, et al., 2015). Sharing the pain of others could therefore also be possible in the absence of first-hand nociception, which is important in the context of shared representations between one's own and empathic pain experiences. Our results indicate that previously found empathy-related activations of sensorimotor processes do not necessarily indicate a specific sharing of another's pain in one's own pain processing system. In fact, a meta-analysis by Lamm et al. (2011) proposed that previously reported somatosensory activation during empathy for pain could reflect "rather unspecific co-activation elicited by the display of body parts being touched rather than a specific matching of the other's

somatosensory and nociceptive state" (p. 2499), as this activation was observed bilaterally and for painful and non-painful stimulation in the meta-analysis (but see also Keysers et al., 2010). In line with this argumentation, Keysers et al. (2004) found S2 (but not S1) to be active during both first-hand and empathy for touch, which matches our results on the first-hand placebo analgesia effect being represented only in S2.

Our findings are also in line with studies about patients with CIP (Danziger et al., 2006, 2009) who found intact empathic responses in this patient group, located in aMCC and AI as well as ventromedial prefrontal cortex and posterior cingulate. This highlights that people with CIP, who cannot use their own somatosensory experience of pain to understand someone else's pain, can still rely on an affective representation and empathize in a similar way as people without this disorder. Affective responses to another's pain may relate to the processing of the emotional significance of aversive stimuli.

Raising again the active debate about the specificity of regions such as aMCC and AI for pain, an alternative explanation for observed activation in these regions could be the general processing of saliency rather than specific processing of pain. For example, painful stimuli would recruit those regions to a stronger degree than non-painful stimulation. In this argument, viewing a potentially damaging threat would be recognized as highly significant, independent of the target (Legrain et al., 2011; Rütgen, Seidel, Riečanský, et al., 2015; Singer et al., 2004; but see also the discussion by Krishnan et al., 2016 and recent contradictory results by Zhou, Li, Zhao, Xu, Zheng, Fu, Yao, et al., 2020b on shared brain representations for first-hand vs. empathic pain). However, differentiating pain from salience was not the main aim and beyond the scope of this paper.

Sharing of another individual's pain might be especially focused on its affective aspects, when a fast and effective processing of the situation does not necessarily require specific somatosensory-related knowledge of pain. In our task, the perception of how unpleasant or

aversive the stimulation was for the other, i.e., a general processing of that pain and its related affective consequences, might have been a more relevant dimension than the exact location of that pain (i.e., the hand). Future studies may thus want to differentiate between situations when observing another person in pain is merely related to affective sharing per se, versus a prompt for specific knowledge about another's pain, such as when specific helping behavior is required. For instance, it may make a difference if participants are only asked to "resonate" with the pain of others without any specific request, as in our study, compared to a setup simulating e.g., the work of medical professions, where it does not suffice to resonate with the affective response but where the exact source of the pain is of higher relevance. A recent review suggested that sensorimotor activations to another's pain could also reflect "activation of defensive responses in agreement with the goal of pain", in order to protect the body from external harm (Riečanský & Lamm, 2019, p. 970). Those responses could thus be seen as less relevant when the situation is known to be unpleasant and aversive but does not require helping behavior. This may also explain the discrepancy of our findings with a recent study finding a causal role of S1 in driving prosocial behavior (Gallo et al., 2018).

In addition to this reasoning, previous studies showing a role of sensorimotor or somatosensory brain regions in pain empathy used a) salient video stimuli depicting painful needle injections into body parts and/or b) different setups and instructions, specifically prompting participants to reason about the sensory consequences of the stimulation and direct their attention to the specific, affected body part (Avenanti et al., 2005, 2006; Bufalari et al., 2007; Lamm, Nusbaum, et al., 2007; Motoyama et al., 2017). Despite our findings, i.e. an absence of evidence for somatosensory sharing, we therefore cannot completely rule out the possibility of still having missed somatosensory involvement with our design, since most of the studies reporting somatosensory brain activation in response to empathic processing used picture-based tasks where explicit images of limbs in painful situations are shown, while we

used electrical stimulation in the present study (Lamm et al., 2011 for a meta-analysis; Xiang et al., 2018 for a review). Our design can thus both be seen as a strength and a limitation: By experiencing the pain first-hand, participants should have a clear representation of how the stimulation feels for the other person, which should amplify the empathic response. However, the still rather abstract nature of the stimuli (as compared to needles penetrating the skin) could have diminished the response. Another limitation of the present study is the fact that we jointly modelled the long, jittered anticipation period and the short delivery periods (in line with Rütgen, Seidel, Silani, et al., 2015). Due to the dominance of affective anticipatory processing within the analyzed time bin, our model could have exaggerated affective responses to the pain and hidden any somatosensory effects. Indeed, an ERP setup used e.g., in Bufalari et al. (2007) would have been better suited to for detecting somatosensory responses than a combination of our task with fMRI. We are currently investigating this possibility in a separate study employing a typical picture-based paradigm, which should aid in shedding further light on this issue. Furthermore, we pre-selected our sample to include only placebo responders in order to investigate a transfer of this effect to empathy. This was a necessary precondition for making any conclusions regarding how placebo effects in one domain (first-hand experience) transfer to another one (empathy). Our findings are thus limited to this type of sub-sample.

However, finding complementary results in both behavior and brain responses and further evidence in our post hoc analyses, we are confident in our conclusion that the somatosensory component of pain does not play a causal role in pain empathy, in the present design.

3.2.7 Conclusion

Our findings suggest a robust localized placebo analgesia effect for first-hand pain, but no evidence for a role of the sensory-discriminative component in empathic sharing. Nevertheless, we observed shared brain activations between first-hand and empathy for pain

in the affective-motivational component. Using a causal-experimental manipulation and a tailored design, empathy for another person was not influenced by a localized pain reduction in a specific body part, thereby not confirming our preregistered predictions. These insights are important when trying to characterize the magnitude of influence that our own pain experience has on our ability to empathize and suggest that empathy for pain, at least when investigated with the type of paradigms used here and previously, may rely more on sharing of another's affective, compared to their somatosensory state.

3.2.8 Acknowledgements

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3.2.9 Author contributions

Helena Hartmann: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Software, Visualization, Writing - original draft, Writing - review & editing. **Markus Rütgen:** Formal analysis, Methodology, Supervision, Writing - original draft, Writing - review & editing. **Federica Riva:** Formal analysis, Supervision, Writing - original draft, Writing - review & editing. **Claus Lamm:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing - original draft, Writing - review & editing.

3.2.10 Declarations of interest

None.

3.2.11 Funding

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3.2.12 Supplement A

Sample

Exclusion criteria were past or present enrolment in academic studies including psychology, pharmaceutics or (veterinary, dental, human, etc.) medicine (due to prior knowledge about deceptive elements of the study setup), any neurological or psychiatric conditions, past or present self-injurious behavior, past or present medical conditions regarding the hands or the skin on the hands that might interfere with current pain sensitivity (e.g. numbness, chronic pain, trauma or injuries, or long-term pain therapy), past or present substance abuse (alcohol or drugs), the intake of psychopharmacological medication (besides oral contraceptives) within the last three months, left-handedness or no handedness preference, and a weakness in distinguishing right from left. Handedness was assessed with a combination of two handedness questionnaires (Büsch et al., 2009; Oldfield, 1971). As suggested by Tran et al. (2014), a laterality quotient (LQ; going from -100 = strongly left-handed to +100 = strongly right-handed) was calculated out of the ten most selective items of both questionnaires, and only individuals with LQs of 72 or higher were invited to the study. A weakness in distinguishing right from left was operationalized as answering the question "How often do you mix up left and right in your daily life (e.g., while making a turn with the car)?" with either 'sometimes', 'often' or 'always'. We tested each participant twice for the contraindications regarding MRI scanning, once via the online screening questionnaire and

once face-to-face at the outset of the scanning session. Dropouts, including placebo analgesia nonresponders, were replaced until the calculated sample size of 45 participants was reached.

Nonresponder identification

Nonresponders in regard to the placebo manipulation were determined using four exclusion criteria. First, any verbally expressed doubts regarding the study setup were recorded during and after the session and followed up on. In case of vague doubts, participants were asked to specify their doubts as much as possible. Second, we assessed belief scores about the effectiveness of the medication to decrease pain at three time-points during the session (after the medical cover applied the gel = pre-conditioning, after the conditioning procedure = post-conditioning, and after the completion of all tasks = post-session). Low beliefs in general (pre- and post-conditioning ratings each on a continuous visual-analogue-scale from 0-10 cm, sum of both ratings < 6.66 cm) and strong decreases between the first and the second time-point (pre- minus post-conditioning ratings > 3.33 cm) indicated a lack of responding. Third, we took the number of needed conditioning trials into account. If participants responded with a rating higher than 5 to the conditioning stimulus on the right hand (given at a medium intensity of 4) and/or with a rating of 5 or lower to the stimulus on the left hand (given at a high intensity of 7), the trial was deemed unsuccessful and repeated. It should be noted here that none of the tested participants needed more than three conditioning trials. Finally, due to the within-subjects design of this study, we were able to directly compare the first-hand pain ratings of the left and right hand and use them as an additional exclusion criterion.

Procedure

To ensure equal conditions for all participants and to strengthen the cover story, we instructed participants to refrain from alcohol, drugs, or medication-intake 24 hours before the session as well as from intake of food or any other drink but water one hour before the

session. Participants were told that the gel was already well established regarding its effectiveness, but we were interested in its neural representation.

For the placebo induction we used a combination of verbal suggestions and classical conditioning techniques. First, the medical cover (who was either male or female) did a short medical screening including a (pseudo) drug-test to increase believability of the cover story, after which he/she explained the pain-reducing effects of the "medication" and gave further information on the duration of action, use and side-effects. The "medication" was presented to the participants as a "potent, local anesthetic" with strong pain-reducing effects only on the part of the skin it is applied to. We used the term "anesthesia" rather than "analgesia" in the instructions to increase believability, as the placebo was a topical gel. Furthermore, the "medication" was presented as being well established and legally approved since many years, as well as frequently and routinely used for chronic pain patients and in dental procedures. As a side-effect in very rare cases, dry skin and slight irritation was mentioned. To avoid decrease of beliefs due to an absence of "numbing", participants were told that the medication blocked pain receptors pharmacologically and thus would exert no effects on normal touch sensitivity or non-painful stimulation. Participants were further told that the effectiveness of the medication would be tested after the waiting time by means of a brief pain test from the experimenters before going into the scanner. If the participant had no more questions, the medical cover first applied the placebo gel on the whole dorsum of the right hand (on which the medical cover had previously attached a white paper bracelet to visually remind the participants of their "treated" hand) and directly after that a control gel with no active ingredients on the left hand. The medical cover explained to the participants that this was routinely done to ensure equal conditions for the two hands and make them comparable for later analysis. He/she further explained that the inactive gel on the left hand represented a basis for the participant's normal pain perception in the study (the word "placebo" was never

mentioned). To compare brain activation of all participants in the group analysis later on, the placebo gel was applied on the dominant, right hand and the control gel on the left hand in all participants. Both gels contained 0.5 g Carbomer, 0.09 g TRIS, 15 g undiluted Isopropanol, 3 g Glycerol, 10 g Propylenglykol and Aqua pur. ad 100 g. The only difference was 10 g (out of 100 g) more Isopropanol in the placebo gel and 10 g basic skin cream ('Ultrasicc') instead of Isopropanol in the control gel to change visual and olfactory properties.

In the scanner room, the confederate was told that she should communicate with gestures during the experiment because the microphone was built inside the scanner bore. These instructions were given in front of the participant to further enhance the belief that the confederate was in fact a second participant. In general, previously used procedures were used to ensure believability of the whole setup, e.g., ensuring contact every now and then between confederate and participant, attaching fake electrodes to the confederate's hands, conducting fake electrode tests with the confederate to check whether they were adhered to the skin correctly, and communicating with both participants equally during the scanning breaks. However, the confederate never received any electrical stimulation, covertly left the scanner room before the scanning started, stayed in the control room with the experimenters during the scanning and exited the building before the participant came out of the scanner. In case of breaks in between runs or emergencies, the confederate was secretly asked to return to her table next to the scanner as if she had been sitting there during the task. To avoid habituation of the skin where the electrodes were attached and confusion of painful and non-painful stimulation, we applied one additional electrode on each dorsum of the hand for delivery of the non-painful stimulation. All four electrodes were tested with the participant lying down by giving low intensity stimulation on each electrode to ensure optimal skin adherence. The value for non-painful stimulation calibrated outside of the scanner was

therefore tested on the new electrodes and if rated too low or high, slightly adjusted for each hand to represent a subjective rating of 1 = "not painful, but perceivable".

Pain task

The visual stimuli of participant's and confederate's hands were created with a Leica D-Lux 54 in the first session. Hands resting on a black cardboard were photographed from the top in similar lighting conditions. The confederate stimuli were created in the same way, but without the white bracelet to indicate no medication. The stimuli were then edited with Photoshop CC and Microsoft PowerPoint, removing the background, and inserting target and hand cues in either red (RGB = 255/0/0, HEX = #FF0000) or blue (RGB = 0/0/255, HEX = #0000FF). The final stimuli were rescaled to 900x627 pixels for the task. During the scanning, the task was displayed on a BOLD screen 32 LCD for fMRI (https://www.crsltd.com/tools-for-functional-imaging/mr-safe-displays/boldscreen-32-lcd-for-fmri/nest/boldscreen-32-technical-specification#npm) that the participant viewed over a mirror mounted on the head coil.

Analyses and plotting

For our analyses and plotting in RStudio, we used the following packages (and functions): stats (shapiro.test, t.test, cor.test, aggregate), ez (ezANOVA), BayesFactor (ttestBF), plyr (ddply), dplyr (arrange), tidyr (gather, spread), reshape2 (dcast), yarrr (pirateplot) and ggplot2 (ggplot). Figures 3 and 5 were created in Python/Jupyter Notebook using the Nilearn module (functions: plot_anat, add_contours and plot_glass_brain; https://nilearn.github.io/index.html).

Behavioral results

In order to evaluate the strength of the subjective placebo effect in our sample, we conducted two manipulation checks. The first check was preregistered as exploratory, the second one was added post hoc to get a better impression of the subjective pain experience on

each hand when asked at the end of the session. First, we investigated differences between the three ratings of the placebo gel effectiveness. Mean ratings were $M \pm SD = 6.64 \pm 1.80$ after the administration of the gel (pre-conditioning), 8.06 ± 1.27 after the conditioning procedure (post-conditioning) and 6.71 ± 2.62 at the end of the testing session (post-session; see manipulation checks a1 and a2 in Figure 2 in the main text and Figure Figure *9* here).

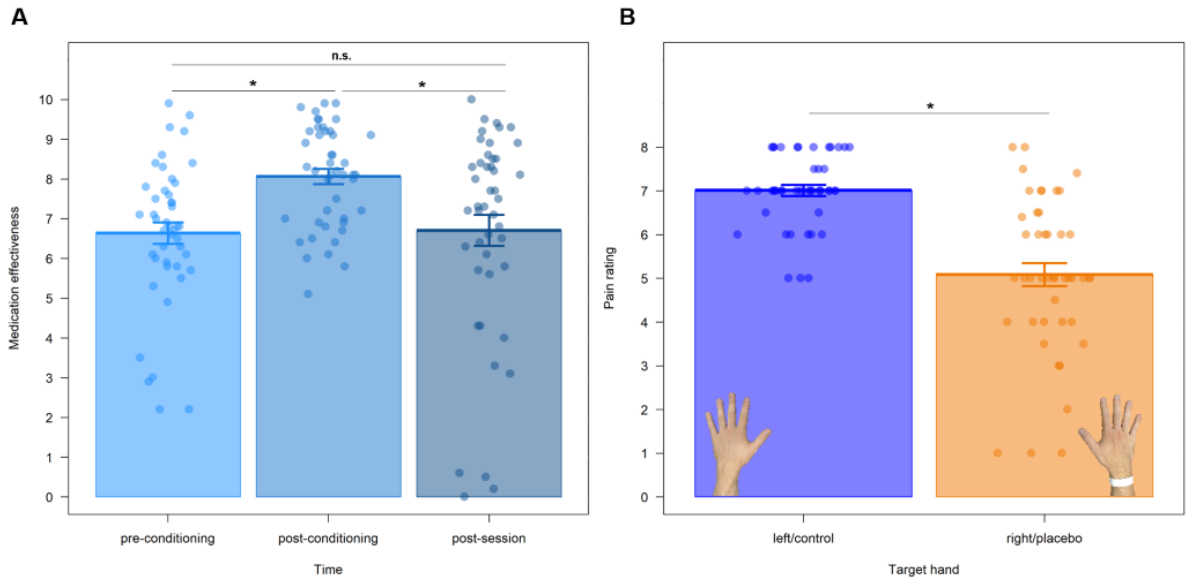

Figure 9. We conducted two behavioral manipulation checks evaluating the strength of the first-hand placebo effect. Displayed are means and standard errors of the mean. A) Beliefs in the effectiveness of the administered placebo gel at three time points during the experiment: after the topical application by the medical cover (pre-conditioning), after the conditioning procedure (post-conditioning) and during the debriefing at the end of the session (post-session). This revealed a significant increase of beliefs after the conditioning. Although the beliefs significantly decreased until the end of the session, they did not drop significantly lower than initial belief levels. B) Average intensity of the painful stimulation received on each hand judged at the end of the session. Here, we observed significantly lower pain ratings for the placebo compared to the control hand. Figure taken from the Supplementary Material of Hartmann, Rütgen, Riva, et al. (2021).

Significant differences emerged between the pre- and post-conditioning ratings ($t(44) = 5.91$, $p < .001$, $M_{diff} = 1.42$, 95% $CI_{meandiff}$ [0.94, 1.91]), as well as between the post-conditioning vs. post-session ratings ($t(44) = -3.80$, $p < .001$, $M_{diff} = -1.36$, 95% $CI_{meandiff}$ [-2.07, -0.64]). No significant differences were found between the pre-conditioning vs. post-session ratings ($t(44) = 0.16$, $p = 0.875$, $M_{diff} = 0.07$, 95% $CI_{meandiff}$ [-0.78, 0.92]). This indicated that effectiveness beliefs in the "medication" increased significantly from gel administration to the conditioning procedure. Furthermore, participants' beliefs in the

"medication" dropped after the completion of the task, but it did not drop lower than the initial effectiveness belief after gel administration when asked at the end of the session. Second, we evaluated the difference between average stimulation intensities felt on each hand when asked after the session and found a significant difference between the placebo ($M \pm SD$ = 5.08 ± 1.76) and the control hand ($M \pm SD$ = 7.01 ± 0.84): $t(44) = -8.11$, $p < .001$, $M_{diff} = -1.93$, 95% $CI_{meandiff}$ [-2.41, -1.45]. Participants recalled feeling less pain on their right placebo hand compared to their left control hand during the task. Both manipulation checks therefore showed evidence for a subjective localized placebo effect over the whole course of the session that was highest right before the completion of the pain task.

Table 2

Behavioral results of the ANOVA using self- and other-related pain ratings

Effects	$F_{(1,44)}$	$p_{(two\text{-}tailed)}$	*gen.* η^2
target	72.15	< .001	0.13
hand	18.44	< .001	0.04
intensity	840.67	< .001	0.84
target x hand	20.11	< .001	0.04
target x intensity	9.31	< .001	0.03
hand x intensity	61.54	< .001	0.05
target x hand x intensity	67.58	< .001	0.05

Table 3

Behavioral results of the ANOVA using unpleasantness ratings

Effects	$F_{(1,44)}$	$p_{(two\text{-}tailed)}$	*gen.* η^2
hand	1.38	.246	0.001
intensity	167.89	< .001	0.42
hand x intensity	0.48	.490	< 0.001

fMRI results

Table 4

fMRI whole brain results for manipulation check b1 (first-hand pain network).

Clusters and brain regions	h	*x*	*y*	*z*	*t* value	*p* value
Cluster 1 (*k* = 7390)						< .001
insula	R	38	-14	20	10.13	
insula	R	44	10	-2	9.62	
insula	R	38	4	-10	8.12	
Cluster 2 (*k* = 15677)						< .001
midcingulate cortex	M	0	8	40	9.54	
anterior cingulate cortex	R	2	24	28	9.42	
midcingulate cortex	M	0	16	34	9.37	
Cluster 3 (*k* = 10468)						< .001
cerebellar vermis 6	M	0	-56	-22	8.07	
cerebellar vermis 6	R	2	-76	-18	7.80	
cerebellum	L	-32	-52	-30	7.72	

Note. Significant clusters resulting from the contrast [*self - pain > self no pain]* in the left control hand including hemisphere h, cluster size *k*, MNI coordinates x, y, z, *t* value and *p* value (whole brain, FWE-corrected at $p < .05$, cluster level, $k > 188$). Brain regions were labelled with the Anatomy toolbox version 2.15 (Eickhoff et al., 2005).

Table 5

fMRI SVC results for manipulation check b2 (placebo analgesia network).

Contrasts and brain regions	h	*k*	*x*	*y*	*z*	*t* value	*p* value
Control hand > placebo hand							
S2	R	509	38	-16	20	13.37	< .001
posterior insula	R	399	38	-14	12	8.72	< .001
dACC	R	386	4	2	42	7.22	< .001
dACC	L	256	-10	2	40	3.54	.019
anterior insula	L	152	-36	24	8	4.46	.001
anterior insula	R	129	38	10	6	6.12	< .001
thalamus	R	26	14	-14	8	3.77	.003
Placebo hand > control hand							
DLPFC	R	244	28	14	48	5.29	< .001
S2	L	175	-38	-18	20	4.90	< .001

Note. Significant clusters resulting from the contrasts [*self - pain - control hand > self - pain - placebo hand]* and [*self - pain - placebo hand > self - pain - control hand]* including hemisphere h, cluster size *k*, MNI coordinates x, y, z, *t* value and *p* value (small volume correction (SVC), FWE-corrected at $p < .05$, peak-level). Only the highest peak is included in case of several peaks in a cluster. Brain regions were labelled with the Anatomy toolbox Version 2.15 (Eickhoff et al.,

2005). S2 = secondary somatosensory cortex; aMCC = anterior midcingulate cortex; DLPFC = dorsolateral prefrontal cortex.

Table 6

fMRI whole brain results for manipulation check b2 (placebo analgesia network).

Contrasts, clusters, and brain regions	h	*x*	*y*	*z*	*t* value	*p* value
Control hand > placebo hand						
Cluster 1 (*k* = 16941)						< .001
rolandic operculum (OP3)	R	38	-16	20	13.37	
postcentral gyrus (3b)	R	26	-40	68	10.16	
precentral gyrus	R	30	-20	74	8.92	
Cluster 2 (*k* = 3485)						< .001
cerebellum (VIII)	L	-26	-44	-50	8.56	
cerebellum (IV-V)	L	-26	-42	-30	7.21	
cerebellum (VI)	L	-26	-56	-24	6.52	
Cluster 3 (*k* = 702)						< .001
rolandic operculum	L	-50	8	2	4.58	
insula	L	-36	24	8	4.54	
insula	L	-38	8	0	3.92	
Cluster 4 (*k* = 442)						.001
supramarginal gyrus	L	-52	-38	28	5.50	
supramarginal gyrus	L	-64	-48	28	3.70	
Cluster 5 (*k* = 270)						.011
middle frontal gyrus	L	-30	40	32	4.02	
Placebo hand > control hand						
Cluster 1 (*k* = 2046)						< .001
angular gyrus	R	38	-54	38	5.47	
superior parietal lobule	R	34	-72	50	4.91	
superior occipital gyrus	R	36	-74	48	4.72	
Cluster 2 (*k* = 1533)						< .001
calcarine gyrus	R	12	-90	6	5.40	
fusiform gyrus	R	28	-76	-10	5.08	
lingual gyrus	R	26	-72	-2	4.71	
Cluster 3 (*k* = 1466)						< .001
postcentral gyrus (4a)	L	-36	-32	66	6.20	
paracentral lobule	L	-16	-20	30	4.68	
paracentral lobule	L	-10	-20	60	4.67	
Cluster 4 (*k* = 439)						.001

middle frontal gyrus	R	28	14	48	5.29	
Cluster 5 (k = 299)						.007
inferior frontal gyrus (p. triang.)	R	46	34	24	4.38	
middle frontal gyrus	R	52	32	32	4.31	
Cluster 6 (k = 277)						.010
angular gyrus	L	-34	-62	42	4.02	
Cluster 7 (k = 200)						.039
rolandic operculum	L	-38	-18	20	4.90	

Note. Significant clusters resulting from the contrasts [*self - pain - control hand* > *self - pain - placebo hand]* and [*self - pain - placebo hand* > *self - pain - control hand*] including hemisphere h, cluster size *k*, MNI coordinates x, y, z, *t* value and *p* value (whole brain, FWE-corrected at $p < .05$, cluster-level, $k > 188$). Brain regions were labelled with the Anatomy toolbox Version 2.15 (Eickhoff et al., 2005).

Table 7

ANOVA using pooled activation of all seven ROIs (lAI, rAI, aMCC, lS1, rS1, lS2, rS2).

Effects	*df*	*F*	$p_{(two\text{-}tailed)}$	*gen.* η^2
target	1,44	197.03	< .001	0.24
hand	1,44	6.48	.014	0.004
intensity	1,44	29.58	< .001	0.03
roi^S	6,246	27.61	< .001	0.11
target x hand	1,44	1.86	.179	0.001
target x intensity	1,44	6.45	.015	0.005
hand x intensity	1,44	0.61	.439	< 0.001
target x roi^S	6,246	31.41	< .001	0.05
hand x roi^S	6,246	20.08	< .001	0.01
intensity x roi^S	6,246	13.86	< .001	0.01
target x hand x intensity	1,44	0.07	.789	< 0.001
target x hand x roi^S	6,246	12.79	< .001	0.01
target x intensity x roi^S	6,246	6.97	< .001	0.006
hand x intensity x roi^S	6,246	2.33	.033	0.001
target x hand x intensity x roi^S	6,246	1.01	.419	< 0.001

Note. Effects marked with an "S" had a significant Mauchly's test for sphericity and corresponding *p*-values are reported using Greenhouse Geisser sphericity correction. The following regions of interest were included: l/rAI = left/right anterior insula, aMCC = anterior midcingulate cortex, l/rS1 = left/right primary somatosensory cortex, l/rS2 = left/right secondary somatosensory cortex.

Table 8

ANOVA of left anterior insula.

Effects	$F_{(1,44)}$	$p_{(two\text{-}tailed)}$	*gen.* η^2
target	107.71	< .001	0.21
hand	7.70	< .001	0.009
intensity	25.52	.008	0.04
target x hand	3.12	.084	0.004
target x intensity	0.91	.345	0.001
hand x intensity	4.09	.049	0.003
target x hand x intensity	0.39	.533	< 0.001

Table 9

ANOVA of right anterior insula.

Effects	$F_{(1,44)}$	$p_{(two\text{-}tailed)}$	*gen.* η^2
target	195.91	< .001	0.39
hand	5.51	.023	0.008
intensity	32.72	< .001	0.06
target x hand	2.51	.121	0.003
target x intensity	4.09	.049	0.006
hand x intensity	0.004	.984	< .001
target x hand x intensity	0.33	.570	< .001

Table 10

ANOVA of anterior midcingulate cortex.

Effects	$F_{(1,44)}$	$p_{(two\text{-}tailed)}$	*gen.* η^2
target	138.25	< .001	0.30
hand	2.84	.099	0.003
intensity	27.63	< .001	0.05
target x hand	2.84	.099	0.003
target x intensity	5.40	.025	0.008
hand x intensity	0.08	.779	< 0.001
target x hand x intensity	0.10	.753	< 0.001

Table 11

ANOVA of left secondary somatosensory cortex.

Effects	$F_{(1,44)}$	$p_{(two\text{-}tailed)}$	*gen.* η^2
target	119.63	< .001	0.39
hand	3.84	.056	0.006
intensity	31.73	< .001	0.08
target x hand	7.50	.009	0.01
target x intensity	50.34	< .001	0.07
hand x intensity	3.37	.073	0.005
target x hand x intensity	0.33	.569	< 0.001

Table 12

ANOVA of right secondary somatosensory cortex.

Effects	$F_{(1,44)}$	$p_{(two\text{-}tailed)}$	*gen.* η^2
target	110.67	< .001	0.34
hand	135.35	< .001	0.13
intensity	22.63	< .001	0.06
target x hand	64.66	< .001	0.08
target x intensity	42.98	< .001	0.05
hand x intensity	5.66	.022	0.008
target x hand x intensity	3.48	.069	0.005

Table 13

ANOVA of left primary somatosensory cortex.

Effects	$F_{(1,44)}$	$p_{(two\text{-}tailed)}$	*gen.* η^2
target	16.51	< .001	0.05
hand	12.86	< .001	0.02
intensity	0.18	.678	< 0.001
target x hand	7.54	.008	0.01
target x intensity	0.59	.447	0.001
hand x intensity	0.03	.874	< 0.001
target x hand x intensity	0.15	.698	< 0.001

Table 14

ANOVA of right primary somatosensory cortex.

Effects	$F_{(1,44)}$	$p_{(two\text{-}tailed)}$	*gen.* η^2
target	37.40	< .001	0.12
hand	5.40	.025	0.008
intensity	0.11	.742	< 0.001
target x hand	0.62	.435	< 0.001
target x intensity	0.59	.446	0.001
hand x intensity	0.21	.645	< 0.001
target x hand x intensity	0.002	.967	< 0.001

The following analyses were added over the course of the revisions in order to refine results and address reviewer comments. Due to null results on the neural level, we added Bayesian *t*-tests of the ROI analyses in order to investigate evidence for the null hypothesis (see Table 15).

Table 15

Overview of the results in the Bayesian t-tests for the seven ROIs.

			BF_{10}		
Region of interest	**MNI coordinates**	**Prior**	self	other	s vs. o
aMCC	-2 23 40	Cauchy (0,1)	0.12	0.13	0.12
lAI	-40 22 0	Cauchy (0,1)	0.13	0.13	0.14
rAI	39 23 -4	Cauchy (0,1)	0.39	0.14	0.14
lS1	-39 -30 51	Cauchy (0,1)	0.12	0.12	0.12
rS1	36 -36 48	Cauchy (0,1)	0.12	0.13	0.13
lS2	-39 -15 18	Cauchy (0,1)	**12.82**	0.12	0.60
rS2	39 -15 18	Cauchy (0,1)	0.61	0.18	0.14

Note. MNI coordinates are given as x, y, and z; AI = anterior insula; aMCC = anterior midcingulate cortex; r/lS1 = right/left primary somatosensory cortex; r/l S2 = right/left secondary somatosensory cortex; BF = Bayes Factor evidence; BF_{10} = evidence for alternative hypothesis (H_1 vs. H_0); s v. o = self vs. other.

Over the course of the revision, it was pointed out by a reviewer that a multivariate analysis of variance (MANOVA) should be a more appropriate analysis approach for the brain data than the one we chose and preregistered (six individual ANOVAs). We thus report results of

the MANOVA below in Table 16. The results are largely congruent with those from the separate ANOVAs.

Table 16

MANOVA including the seven a-priori regions of interest.

Effects	*approx.* $F_{(7,38)}$	*Pillai*	$p_{(two\text{-}tailed)}$
id x target	33.87	0.86	< .001
id x hand	43.84	0.89	< .001
id x intensity	8.93	0.62	< .001
id x target x hand	26.97	0.83	< .001
id x target x intensity	8.77	0.62	< .001
id x hand x intensity	3.60	0.40	.005
id x target x hand x intensity	2.97	0.35	.014

Note. The following regions of interest were included as dependent variables in the MANOVA: Left/right anterior insula, anterior midcingulate cortex, right/left primary somatosensory cortex, right/left secondary somatosensory cortex.

3.2.13 Supplement B

Although our behavioral data did not show a transfer of the placebo analgesia effect to empathy for pain, the ratings for both hands in the empathy condition were qualitatively more similar to the ratings for the placebo hand in the self condition. In other words, although there was no difference in pain ratings between the two hands in the empathy condition, ratings for both hands seemed to be reduced in a similar way as the first-hand ratings for the placebo hand. As a previous study by Rütgen, Seidel, Silani, et al., 2015 only observed this drop of pain empathy ratings in the placebo condition, i.e. no significant difference between self- and other-related ratings in the control condition, we aimed to further explore this "generalized" reduction in pain empathy ratings of both hands and compared ratings of the different conditions using priors derived from that study. This resulted in four Bayesian paired *t*-tests comparing pain ratings in the self/control condition with pain ratings in (a) the other/control condition, and (b) the other/placebo, as well as comparing the self/placebo condition ratings with those of (c) the other/control condition, and (d) the other/placebo condition (priors were

Cohen's *d* effect sizes from the same independent *t*-tests in Rütgen, Seidel, Silani, et al., 2015: a) 0.17, b) 0.76, c) 0.54, d) 0.05; see analysis A4 in Figure 2 in the main text).

Using these priors, we found strong evidence that the other-related pain ratings in the control condition were decreased compared to the control condition in the self (a; $BF_{10} = 2.58 \times 10^6$). This decrease was similar for the other/placebo ratings (b; $BF_{10} = 2.78 \times 10^6$). In line with this, we did not find evidence for a difference in ratings between the self/placebo and other/control conditions (c; $BF_{10} = 0.27$). Finally, similar to Rütgen, Seidel, Silani, et al., 2015, we observed comparable ratings in the placebo conditions for self and other (d; $BF_{10} = 0.85$). In other words, the placebo induction reduced the self- and other-related pain ratings to a similar extent in our study, as reported by Rütgen, Seidel, Silani, et al. (2015), but we report an additional reduction of empathy ratings for the control hand. These findings are in sharp contrast to the previous study which did not find such a decrease in the other-related control condition. In sum, although our initial predictions regarding a localized transfer to empathy were not confirmed, we found that placebo analgesia affected empathic responses in a generalized way. Specifically, we observed lower other-related pain ratings for both hands that were more similar to the self-related pain ratings of the placebo hand. We now want to discuss these results in relation to the results by Rütgen, Seidel, Silani, et al. (2015).

This mismatch of results could be explained by an inherent limitation of our within-subjects design and the effects of placebo analgesia on endogenous opioids. The opioid system generally mediates pain processing (Baumgartner et al., 2006; Karjalainen et al., 2017) and plays an important role during placebo analgesia (Büchel et al., 2014; Colloca, 2019; Eippert et al., 2009; Zubieta et al., 2005), but is also involved during empathic responses to others in pain (Rütgen, Seidel, Silani, et al., 2015; Rütgen et al., 2018). During placebo analgesia, two types of expectancies should be differentiated (Atlas & Wager, 2014; Geuter et al., 2017; Montgomery & Kirsch, 1996). While treatment-related expectancies

relate to the overall knowledge of the context and general subjective beliefs, likely depending on sustained mechanisms such as affective shifts and tonic opioid binding (Atlas et al., 2010; Atlas & Wager, 2012), stimulus-related expectancies are hypothesized to adapt flexibly based on discrete events by depending on transient, phasic responses in systems involved in processing e.g. prediction errors (Atlas et al., 2010). For instance, Atlas and Wager (2014) provided meta-analytic evidence that treatment expectancies are significantly more likely to reduce activation in left insula than stimulus-dependent expectancies.

The within-subjects, localized placebo analgesia induction in our study could therefore have led to two distinct responses: 1) An initial tonic endorphin release over the endogenous opioid system, increasing baseline endorphin levels throughout the whole experiment. This increase, acting as a natural analgesic, might have downregulated emotional arousal and/or the affective response in general (see e.g. Benedetti & Amanzio, 2013 for a review); 2) A phasic modulation adapting flexibly depending on the location of the expected task stimulus (placebo vs. control hand, self vs. other). Such an increased tonic response in the placebo condition might have been an advantage for the previous between-subjects study who was able to induce these changes specifically in the placebo group, with the control group staying at baseline endorphin levels (Rütgen, Seidel, Silani, et al., 2015). This, in turn, could have eased the detection of modulation of affective responses. In our study, however, all participants underwent a placebo analgesia induction and could have experienced this tonic endorphin increase, possibly leading to a generalized down-regulated response. Our results therefore additionally provide tentative evidence for shared affective representations in the form of a generalized placebo analgesia response during empathy for pain. This idea of a primarily tonic placebo effect compared to a phasic modulation is bolstered by our Bayesian analyses showing a generalized decrease of other-related pain ratings of both hands down to the levels of the self-related placebo decrease and contradicts our initial hypothesis of a more

phasic, localized response in regard to stimuli applied specifically to the placebo hand. Our within-subjects design could therefore have hindered us from observing modulation of the affective and/or somatosensory component exactly for this reason. This would then explain why we only partly replicated the behavioral, but not the fMRI results of Rütgen, Seidel, Silani, et al. (2015) regarding a placebo-induced decrease in brain regions related to the affective-motivational component for first-hand or empathic pain.

If this theory holds, however, we should also have observed a generalized/tonic response for first-hand painful experiences. Although we found evidence for a strong localized placebo effect and thus involvement of the phasic component on the behavioral level, we observed no placebo-induced decrease in brain regions related to the affective-motivational component of first-hand pain processing (except for a trend in left AI). However, this inconsistency could e.g. be explained by easier discrimination between one's own hands, i.e. higher saliency of first-hand compared to empathic experiences (see Borsook et al., 2013; Eisenberger, 2015 for critical discussions; Krahé et al., 2013; Legrain et al., 2011). These prerequisites could have allowed for a more phasic modulation in the self, while this was not or much less the case for the other, where differentiation between the hands might have demanded more complex cognitive processing.

In sum, the contribution of a "tonic placebo response" to pain processing might have had a much higher weight in our study than phasic modulatory differences between targets and hands. Our results therefore speak for an affect-modulating role of the opioid system (Nummenmaa & Tuominen, 2017) and enhanced situational modifiability of somatosensory responses for the self compared to the other.

3.3 Study 2: Placebo analgesia does not reduce empathy for naturalistic depictions of others' pain in a somatosensory specific way

Helena Hartmann[a], Federica Riva[a], Markus Rütgen[a], & Claus Lamm[a*]

[a] *Social, Cognitive and Affective Neuroscience Unit, Department of Cognition, Emotion, and Methods in Psychology, Faculty of Psychology, University of Vienna, Vienna, Austria*

* *Corresponding author*

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3.3.1 Abstract

The shared representations account postulates that sharing another's pain recruits underlying brain functions also engaged during first-hand pain. Critically, direct causal evidence for this was mainly shown for affective pain processing, while the contribution of somatosensory processes to empathy remains controversial. This controversy may be explained, however, by experimental paradigms that did not direct attention towards a specific body part, or that did not employ naturalistic depictions of others' pain. In this preregistered fMRI study, we aimed to test whether causal manipulation of first-hand pain affects empathy for naturalistic depictions of pain in a somatosensory-matched manner. Forty-five participants underwent a placebo analgesia induction in their right hand and observed pictures of other people's right and left hands in pain. We found neither behavioral nor neural evidence for somatosensory-specific modulation of pain empathy. However, exploratory analyses revealed a general effect of the placebo on empathy, and higher brain activity in bilateral anterior insula when viewing others' right hands in pain (i.e., corresponding to one's own placebo hand). These results refine our knowledge regarding the neural mechanisms of pain empathy and imply that the sharing of somatosensory representations seems to play less of a causal role than the one of affective representations.

3.3.2 Introduction

Neuroimaging studies of empathy for pain have consistently found involvement of a network of brain regions related to affective-motivational processing of pain, such as anterior midcingulate cortices (aMCC) and anterior insula (AI). Other studies have highlighted the importance of sensory-discriminative processing in empathy, e.g., in primary (S1) and secondary (S2) somatosensory cortices (Keysers et al., 2010 for a review; Fallon et al., 2020; Fan et al., 2011; Jauniaux et al., 2019; Timmers et al., 2018 for meta-analyses). Which regions are recruited depends strongly on the type of empathy task employed, in other words, whether the task focus lies on the "live" pain experience of another vs. on pictorial depictions of others' pain (e.g., Lamm et al., 2011). Furthermore, the exact role of the somatosensory component during empathy remains controversially discussed. More specifically, it is unclear whether somatosensory pain processing networks contribute to empathy for pain by means of somatotopic matching, as they do for first-hand pain. This study thus had the following aims: First, and foremost, to investigate shared neural representations during pictorial depictions of others' pain, and second, to resolve whether we specifically recruit somatosensory representations of our right hand, when empathizing with the pain of another person whose right hand is shown to be in pain on a picture. If this were the case, it would shed light on the putative role of shared *somatosensory* representations in empathy for pain and extend our previous findings on effects of placebo analgesia on shared *affective* representations to the domain of picture-based presentations of others' pain.

Empathy constitutes a complex, multi-faceted phenomenon involving cognitive, affective, and behavioral processes and mechanisms (see e.g., Marsh, 2018; Weisz & Zaki, 2018 for recent reviews). Here we refer to empathy as an affective state isomorphic to the affective state of another person that includes a partial and experiential sharing of the other's affective state (de Vignemont & Singer, 2006; Hall & Schwartz, 2019; Lamm et al., 2019; Shamay-

Tsoory & Lamm, 2018). Interestingly, affective and somatosensory brain regions involved in processing empathic pain overlap in part with brain regions that are also active when we experience pain ourselves (Lamm et al., 2011; Singer et al., 2004). Within the so-called shared representations account of empathy, this activation overlap has been taken to suggest that shared representations may underlie such vicarious experiences. In other words, we seem to recruit the same neural substrates when feeling pain ourselves and when empathizing with someone else in pain (Bastiaansen et al., 2009; Bernhardt & Singer, 2012). Although the majority of studies report this overlap of activation in aMCC and AI (Benuzzi et al., 2018; Corradi-Dell'Acqua et al., 2011; Jackson, Brunet, et al., 2006), other studies have pointed to S1 and/or S2 as equally relevant for pain empathy (Avenanti et al., 2005; Bufalari et al., 2007; Fabi & Leuthold, 2017; Gallo et al., 2018; Lamm et al., 2007; Motoyama et al., 2017; Novembre et al., 2015; Riečanský & Lamm, 2019 for a review). Evidence for shared representations was recently also confirmed with multivoxel pattern analyses (MVPA), which pinpointed the mid- to anterior insular cortex and thus patches of cortex largely associated to affective processes as relevant for the sharing of self- and other-related pain representations (Krishnan et al., 2016; Zhou, Li, Zhao, Xu, Zheng, Fu, Yao, et al., 2020a). This raises the important question whether not only previously shown affective but also somatosensory representations of another's pain experience are shared in pain empathy.

Importantly, an overlap in activation, as demonstrated e.g., with fMRI, does not necessarily imply shared underlying functions and has fostered an active debate regarding the existence and location of shared representations underlying first-hand and empathy for pain. Trying to go beyond correlational evidence of shared *activations* towards evidence for shared *representations*, recent studies have made use of causal and/or psychopharmacological manipulations (Gallo et al., 2018; Rütgen, Seidel, Riečanský, et al., 2015; Rütgen, Seidel, Silani, et al., 2015; Rütgen et al., 2018; Rütgen et al., 2021). One such method is placebo

analgesia, the reduction of first-hand pain by means of an inert pharmacological substance, which has been found to decrease both first-hand pain ratings and pain-related brain activity in regions such as insula, ACC, S1, S2 and thalamus (Atlas & Wager, 2014 for a meta-analysis; Eippert et al., 2009; Geuter et al., 2013; Wager et al., 2004; see Colloca et al., 2013; Wager & Atlas, 2015 for reviews). Moreover, placebo analgesia has been successfully employed to downregulate pain via localized manipulations, e.g., using gels or creams on different body parts (Bingel et al., 2006; Geuter et al., 2013; Schafer et al., 2015; Schenk et al., 2014; Wager et al., 2004). Turning to empathy, Rütgen et al. used this method in three consecutive studies to test whether such a first-hand pain reduction transfers to empathy for pain, as the shared representations account would suggest (Rütgen, Seidel, Riečanský, et al., 2015; Rütgen, Seidel, Silani, et al., 2015; Rütgen et al., 2018). Indeed, global placebo analgesia by means of a placebo pill lowered activity in brain regions such as AI, dorsal ACC, S2 and thalamus, thus demonstrating that this induction procedure was indeed able to down-regulate first-hand somatosensory processing (Rütgen, Seidel, Silani, et al., 2015). In the empathy condition, the authors further observed lower ratings of unpleasantness and empathy for pain as well as lower activity in aMCC and left AI in the placebo group compared to a control group who had not received any pill. They further showed a crucial role of the opioid system, as blocking placebo analgesia using the opioid antagonist naltrexone blocked the manipulation's effects on first-hand and empathy for pain. A recent study from our lab showed additional domain-general effects, with placebo analgesia also affecting the first-hand and empathic experience of unpleasant touch, but pain-specific blockage of these effects using an opioid antagonist (Rütgen et al., 2021). The behavioral results for pain have since been replicated by an independent research group using real painkillers (Mischkowski et al., 2016) and extended to empathy for positive emotional states

(Mischkowski et al., 2019). Similarly, hypnotic analgesia decreased brain responses of both self- and other-related pain in right AI and amygdala (Braboszcz et al., 2017).

Notwithstanding the important advances made by this line of research, several points are still unclear: First of all, these studies did not find any placebo-related modulation of the sensory-discriminative component of pain during empathy, suggesting that empathy for pain might be specifically focused on sharing the affective representation of another's pain (Rütgen, Seidel, Silani, et al., 2015). Relatedly, it has been proposed that specific types of empathy for pain paradigms recruit somatosensory brain regions to a larger degree, namely tasks where the attention is directed to the somatic location of pain, such as the exact body part in which the pain is inflicted (Lamm et al., 2011; Xiang et al., 2018; Zaki et al., 2016). Note in this context that two types of paradigms are commonly used in pain empathy research: *cue-based* tasks, which use abstract cues to indicate experimentally induced painful (electrical or thermal) stimulation in different intensities delivered to another person (usually on the hands or arms); and *picture-based* tasks, which show pictures or pre-recorded videos of individuals' body parts or faces in pain. Crucially, cue-based tasks usually employ an additional first-hand pain condition where the participants receive the same stimulation they are empathizing with (either in a separate block, or intermixed with the empathy condition), while picture-based tasks focus mostly on the empathic reaction to visual stimulus material (but see Corradi-Dell'Acqua et al., 2011; Krishnan et al., 2016; Zhou, Li, Zhao, Xu, Zheng, Fu, Yao, et al., 2020b). One main conceptual difference between these paradigms is thus the way one infers the pain of another person, i.e., either "live" vs. via pictorial representations. Furthermore, in cue-based tasks, participants rely on implicit cues representing the target or intensity of the stimulation happening in that exact moment, while picture-based tasks show explicit and directly visible pain events through videos or pictures. Importantly, previous studies on placebo analgesia exclusively used cue-based setups with "live" experienced pain,

and thus did not focus on depictions of others in painful situations (Rütgen, Seidel, Riečanský, et al., 2015; Rütgen, Seidel, Silani, et al., 2015). The present study aimed to close this gap by employing such a picture-based design. Most studies in the past employing picture-based tasks have not employed causal manipulations such as placebo analgesia. Only one line of research used transcranial magnetic stimulation to measure changes in corticospinal motor representations of hand muscles in individuals observing hands or feet being penetrated by needles (e.g., Avenanti et al., 2005; see Keysers et al., 2010 for a review). They showed a reduced amplitude of motor-evoked potentials in the muscles that participants saw being pricked by the needle, which correlated with subjective ratings of sensory pain qualities. This highlights the importance of somatic resonance and a direct, bodily matching of specific sensory aspects of others' pain, leading to our second aim of investigating shared somatosensory representations with our picture-based setup.

We thus conducted a project employing a localized placebo analgesia manipulation on the right hand only (with the left hand acting as a control) and two paradigms tailored to investigate different yet related research questions. The first part of this project published elsewhere (Hartmann, Rütgen, Riva, et al., 2021) aimed to refine the results of Rütgen, Seidel, Silani, et al. (2015) regarding the attentional focus by using an adapted version of their cue-based task, where electrical stimulation was administered either to the participants or a confederate. In this setup, however, while increasing the focus on the affected body part, live pain to another person still had to be inferred via abstract cues indicating how painful stimulation of that body part was. In brief, this task did not reveal evidence for a location-specific somatosensory sharing of others' pain. The second part of this project, reported here, aimed to investigate shared representations in a picture-based task consisting of naturalistic depictions of others in everyday painful situations. Beyond advancing our general understanding how placebo analgesia affects empathy in such a setup, this task also allowed

us to focus on the role of lateralized somatosensory representations, as placebo analgesia had been induced only in the right hand, and the stimuli showed left and right hands. Our previous (Hartmann, Rütgen, Riva, et al., 2021) and the present study thus used the same participant sample to investigate placebo-induced transfers in two distinct tasks that were conducted after each other in the same session.

In sum, it is currently unknown (1) whether shared representations also hold in picture-based empathy paradigms, and (2) whether pain empathy recruits first-hand somatosensory, body part-specific representations of that pain. The goal of the present, preregistered study was therefore to investigate whether locally applied placebo analgesia modulates the behavioral and neural responses to explicit naturalistic depictions of others in everyday painful situations. We tested this by experimentally reducing first-hand pain in one specific body part, the right hand, using a placebo gel. We hypothesized that behavioral and neural responses (both in affective and somatosensory brain regions) would be lower for stimuli corresponding to the right hand, where placebo analgesia was induced, compared to left/control hand stimuli. Our preregistered main predictions were, thus, that neural somatosensory representations engaged by first-hand pain are also recruited when empathizing with the pain of another person, and that the hand-specific reduction of first-hand pain would result in a corresponding hand-specific reduction of empathy for pain. If we indeed observed a location-specific reduction of pain empathy (lower pain ratings and lower brain activity in S1 and S2 for right hand- compared to left hand-related stimuli), this would imply shared representations at the level of *somatosensation*. If, on the other hand, we did not observe any kind of behavioral or neural differences between the left- and right-hand stimuli, it would suggest that somatosensory representations would play no specific role in empathy for pain. Such a finding would however be in line with previous reports on how placebo analgesia affects affective representations, which did not report modulation of somatosensory

activity; as well as with our most recent study within the same sample, which did not find evidence for somatosensory modulation in a cue-based paradigm tailored to engage somatosensory areas.

3.3.3 Materials and Methods

Data and code availability statement

Unthresholded statistical maps are available on NeuroVault (https://neurovault.org/collections/9244/). The stimuli of the picture-based empathy for pain task are available and will be shared individually upon request.

Preregistration

In line with the suggestion for openly stating transparency by Simmons et al. (2012), we report how we determined our sample size, all data exclusions, all manipulations, and all measures in the study. This study was preregistered on the OSF prior to any creation of data (Hartmann et al., 2018; preregistration: osf.io/uwzb5; addendum: osf.io/h7v9p). The here reported part of the project was designed to extend the results of Rütgen, Seidel, Silani, et al. (2015) regarding a transfer of first-hand placebo analgesia to empathy for everyday painful situations. The study design and procedures reported here are therefore largely identical to the ones employed in Hartmann, Rütgen, Riva, et al. (2021), and reproduced here and in the Supplement. In the following methods and results, we clearly separate preregistered procedures and analyses from those added post hoc. Preregistered tests are additionally marked with a 'p' in all results-related figures.

Participants

For estimating the sample size, we conducted an *a priori* power analysis using GPower (Faul et al., 2007), using a conservative average of the lowest effect sizes from previous studies (one-sided paired *t*-test; see Rütgen, Seidel, Riecansky, et al., 2015; Rütgen, Seidel, Silani, et al., 2015). We aimed to detect a medium effect size of Cohen's $d = .40$ at the

standard .05 α error probability with a power of 1-ß = 0.8, yielding a sample size of 41 participants. However, considering that the modulation of placebo analgesia might not be equal for empathy in everyday painful situations, 45 placebo responders was set as the data collection stopping rule. Due to the nature of our research question, it was crucial to obtain a final set of participants who showed a first-hand placebo analgesia effect, in order to investigate a transfer of this effect to empathy for pain. We thus evaluated non-responders to the placebo analgesia manipulation using a set of criteria consisting of three measures already employed in Rütgen, Seidel, Silani, et al. (2015) and a fourth additional criterion possible due to our within-subjects design. In brief, those criteria were 1) strong doubts about the cover story, 2) low belief in the effectiveness of the "medication", 3) a high number of conditioning trials, and 4) higher first-hand pain ratings for the right/placebo compared to the left/control hand in another task (see also sections M.1 in the Supplement for screening and exclusion criteria, and M.2 for nonresponder identification). From a total of 78 recruited participants, we excluded 20 (25.6%) nonresponders to the first-hand pain placebo manipulation, seven due to technical difficulties with the pain stimulator, five due to inconsistent ratings (e.g., equally high ratings for painful and non-painful stimulation in both placebo and control conditions) and/or extensive movement and one participant because of a spontaneously found brain abnormality.

Our final sample included 22 males and 23 females between 19 and 32 years ($M \pm SD_{age}$ = 23.84 ± 2.73, all strongly right-handed with laterality quotients (LQs) ≥ 80 and normal or corrected-to-normal vision). Importantly, this sample of participants also conducted another task in the same session; the findings of this task are published in Hartmann, Rütgen, Riva, et al. (2021). For the purpose of our study, we only recruited strongly right-handed participants and always induced the placebo in the right hand of all participants to avoid laterality-related problems in our fMRI analyses, increase sample homogeneity and retain comparability of the

induction procedure. All participants gave written consent at each outset of their two sessions. Each participant received 50 € for taking part in both sessions and an amount aliquot to their time invested if they dropped out earlier. The study was approved by the ethics committee of the Medical University of Vienna (EK-Nr. 661/2011) and performed in line with the latest revision of the Declaration of Helsinki (World Medical Association, 2013).

Procedure

Participants came to the MRI scanner, where the experimenter explained that the goal of the study was to investigate brain activity associated with a local anesthetic in the form of a medical gel. First, we performed an individual psychophysical pain calibration (a) to determine the maximum level of painful, but tolerable stimulation intensity and (b) to specify average subjective intensities on a visual analogue scale (VAS) from 0 = not painful to 8 = extremely painful for very painful (rating of 7), medium painful (4) and not painful, but perceivable (1) stimulation for the left and right hand separately. Using the procedure employed by Rütgen, Seidel, Silani, et al. (2015), electrical stimulation (stimulus duration = 500 ms) was administered to the dorsum of the hand using the Digitimer DS5 Isolated Bipolar Constant Current Stimulator (Digitimer Ltd, Clinical & Biomedical Research Instruments), one hand at a time, with two rounds going stepwise from very low (0.05 mA) to higher stimulation until the participant indicated the last given stimulus as an 'extremely painful' (rating of 8). In a third round, stimuli with seemingly random intensity in the before calibrated range were delivered (although we alternated intensities corresponding to average ratings of 1, 4 and 7). A few seconds break between each stimulation and a few minutes break between each round ensured a reliable, independent rating of each stimulation.

The calibration was followed by the placebo analgesia induction. To this end, a medical student posing as the study doctor introduced the gel as a "powerful local anesthetic", gave

information on its effects and possible side effects, and then applied the placebo gel on the dorsum of the right hand. Participants were then told that a "control" gel without any active ingredients would be applied on the left hand. In fact, both the placebo and control gel contained nearly the same ingredients and no active pharmacological components (exact ingredients can be found in section M.3 in the Supplement). After 15 minutes of waiting time "for the medication to take effect", we evaluated and amplified the effects of the placebo induction by means of a classic conditioning procedure. As in the calibration, participants were told that they would again receive electrical stimulation to the right or left hand via an attached electrode. Participants thought they would receive stimulation they had rated as very painful before on both hands. This was true for the left/control hand (average intensity rated as 7 during calibration), however, for the right/placebo hand, the experimenter secretly lowered the intensity to medium painful (rating of 4) to suggest pain relief. All participants completed a minimum of two and a maximum of four rounds and received oral feedback by the experimenter after each round. This was done to suggest that participant's ratings on the left/control hand stayed similar to their average ratings during calibration, but the ratings on the right/placebo hand had decreased. This adjustment was done covertly, to maintain a participant's belief that they received equally high intensities on either hand. Importantly, we purposefully chose a within-subjects design and therefore did not directly test whether placebo analgesia leads to a general decrease in somatosensory regions, due to the absence of a control group not undergoing the placebo manipulation.

Afterwards, participants were led into the scanner room and, following general adjustments, completed two fMRI runs of another task (~45 minutes, findings reported in Hartmann, Rütgen, Riva, et al., 2021), and one fMRI run of the picture-based empathy for pain task focused on here (~22 minutes) in a fixed order. Upon completion of all tasks, the

field map and structural image were acquired. The session was concluded with post-experimental questionnaires and took around four hours in total.

Picture-based empathy for pain task

To measure empathy for everyday painful situations, we adapted an established picture-based empathy for pain task from Jackson et al. (2005). Stimuli depicted everyday situations of one person accidently hurting him-/herself. For each situation, four pictures were taken, each picture always depicting both hands of a person taken from a first-person perspective (for the participant), but showing one out of four different conditions: left/control hand pain, right/placebo hand pain, left/control hand no pain, right/placebo hand no pain (see Figure 10A for example stimuli and section M.4 in the Supplement for specific information regarding the stimuli creation and task presentation). A non-preregistered, online validation study was conducted prior to the main study to select 15 situations out of 29 initial ones. To this end, we had recruited an independent sample of 38 right-handed participants (21 females, $M \pm SD_{age} = 30.50 \pm 6.27$). They were asked to rate 116 stimuli (29 situations x 2 intensities x 2 target hands) regarding other-related pain and one's own unpleasantness when viewing the picture, both on 9-point visual analogue scales from 0 = "not at all" to 8 = "extremely painful/unpleasant". From the validation study, 15 out of the 29 situations rated as most painful were selected for the main task and evaluated on the following criteria: i) the stimuli for left and right hand did not differ in the measured dimensions and ii) the stimuli in the pain and no pain conditions did differ from each other. To ensure this, we performed two repeated-measures ANOVAs, for pain and unpleasantness ratings, each including the factors *target hand* (left vs. right hand) and *intensity* (pain vs. no pain) and the ratings from the 15 selected situations (see section M.4 and R.1 in the Supplement for description and results regarding the additionally assessed ratings of arousal, valence, and realism). In the main task, 15 situations per condition were shown, resulting in 60 pictures/trials.

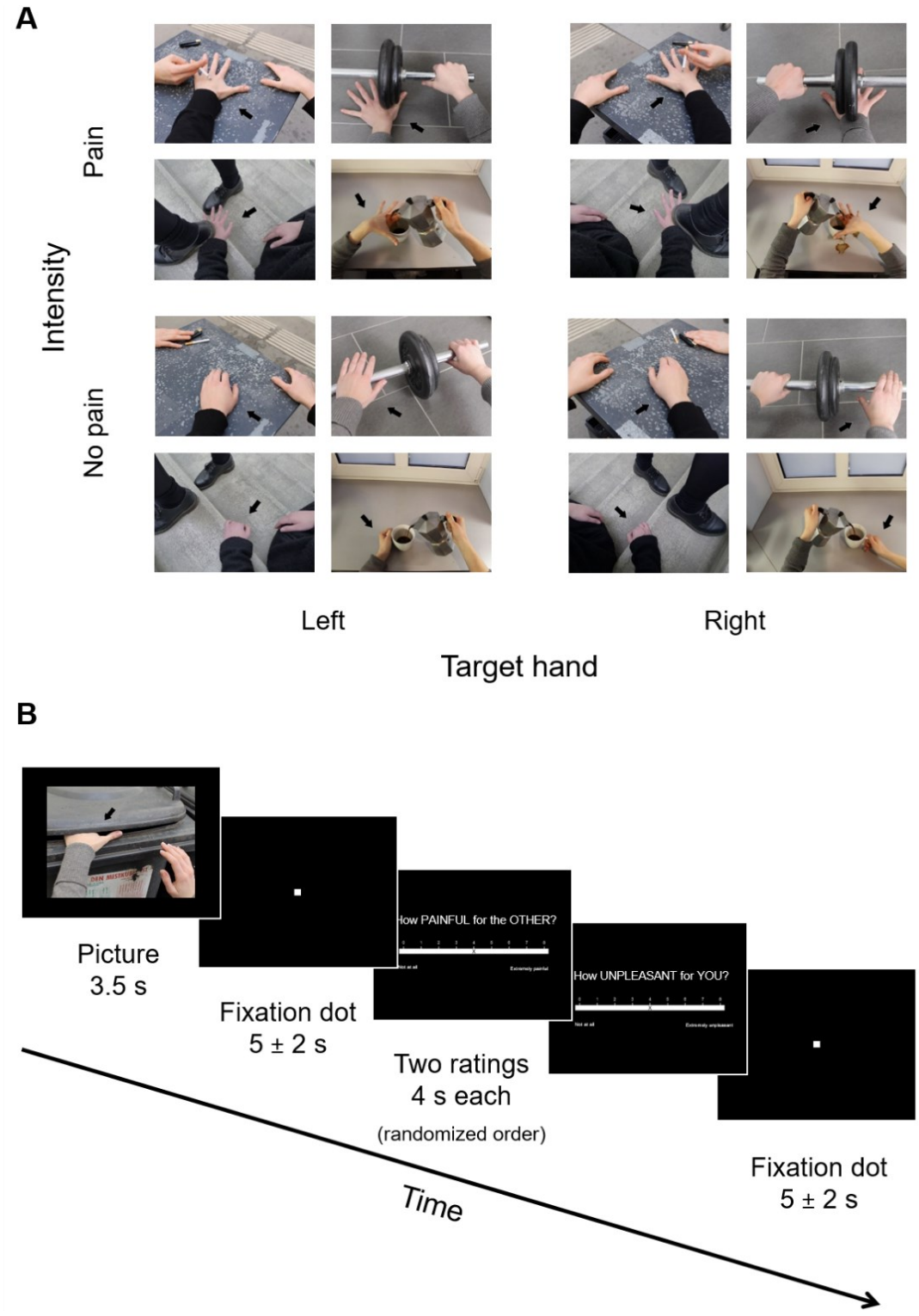

Figure 10. A) Task stimuli showed everyday situations where one person (ostensibly accidentally) hurt him-/herself and varied depending on the target hand (left/control vs. right/placebo) and intensity (pain vs. no pain). Both hands were shown in all stimuli, but black arrows expressly indicated the hand to attend to and to rate in the trial. B) Overview of the picture-based empathy for pain task. In a 2x2 within-subjects design, pictures depicted either painful or non-painful everyday situations, and participants were asked to focus on either the left or right hand (i.e., the one corresponding to their own control or placebo hand, respectively). The hand laterality to be attended to was marked again with a black arrow. Figure taken from Hartmann, Riva, et al. (2021).

The 60 images were included in one out of four pseudorandom trial orders previously created (see Figure 10B for an overview of the trial structure in the task). Each trial consisted of the picture shown centered on a black background for 3500 ms, a jittered waiting period with a white fixation dot on black background for 5000 ± 2000 ms, two rating questions of 4000 ms each played in random order and a jittered inter-trial-interval of 5000 ± 2000 ms, again with a white fixation dot on black background. The hand laterality that the participants had to rate was marked with a black arrow. Tapping into different aspects of empathy (Lamm & Majdandžić, 2015), participants were asked to provide two ratings: (1) "How painful is it for the person in the picture?" and (2) "How unpleasant was it for you to view the picture?". While the former question aimed to measure pain intensity, i.e., the cognitive-evaluative aspect of the others pain, the latter question aimed to capture the affective-sharing aspect of the empathic experience. Questions were rated on the same 9-point scale from 0 = not perceivable to 8 = extremely painful/unpleasant.

Data acquisition

The empathy for pain task was implemented using the Cogent 2000 Toolbox Version 1.33 (http://www.vislab.ucl.ac.uk/cogent_2000.php) within MATLAB R2017b (Mathworks, 2018). MRI data was acquired using a 3 Tesla Siemens Magnetom Skyra MRI-system with a 32-channel head coil (Siemens Medical, Erlangen, Germany). The functional scanning sequence included the following parameters: Echo time (TE) / repetition time (TR) = 34/1200 ms, flip angle = 66°, multi-band acceleration factor = 4, interleaved ascending acquisition, interleaved multi-slice mode, matrix size = 96×96, field of view = 210 mm, voxel size = 2.2×2.2×2.0 mm^3, 52 axial slices coplanar to the connecting line between anterior and posterior commissure, slice gap = 0.4 mm and slice thickness = 2 mm. Functional volumes were acquired in one run of ~22 minutes. Importantly, all participants completed three runs of fMRI data collection in total, with short breaks in between; the data reported here were

always collected in the last run, while findings from the other two runs are reported in Hartmann, Rütgen, Riva et al. (2021). To acquire structural images, we used a magnetization-prepared rapid gradient-echo sequence (TE/TR = 2.43/2300 ms, flip angle = 8°, ascending acquisition, single shot multi-slice mode, field of view = 240 mm, voxel size = 0.8×0.8×0.8 mm^3, 208 sagittal slices, slice thickness = 0.8 mm).

Behavioral data analysis

All behavioral data were processed and statistically analyzed in RStudio Version 3.6.1 (R Core Team, 2020; see section M.5 in the Supplement for information regarding analysis and plotting functions). Preregistered t-tests were conducted one-sided due to a priori, directional hypotheses. Cohen's d's for behavioral and fMRI analyses were calculated using the effect size calculation spreadsheet (version 4.2) provided by Lakens (2013).

Manipulation checks. We conducted two manipulation checks to evaluate the strength of the first-hand placebo analgesia effect. First, we asked participants three times during the session how effective they believed the medication to be in reducing their own pain on the placebo-treated, right hand: after the gel application = pre-conditioning, after the conditioning = post-conditioning and after all tasks in the post-experimental questionnaire = post-session. For this, we conducted three paired t-tests comparing the three time-points with each other. These analyses were preregistered as exploratory, but we expected an increase in belief between pre- and post-conditioning by the conditioning procedure as in Rütgen, Seidel, Silani, et al. (2015). Secondly, we used first-hand pain ratings from the two runs with the cue-based pain task preceding the picture-based task in the same imaging session. There, participants had received and rated electrical stimulation on either hand. As this measure (which was also one of the four preregistered criteria to identify non-responders) was a reliable indicator of placebo analgesia, we also used it here as an additional manipulation check (see also section M.2 in the Supplement). To this end, we conducted a paired t-test

using the first-hand pain ratings from that task (calculated as an index of pain - no pain). We further visually inspected the time course of the ratings related to the right/placebo hand to (a) pinpoint possible decreases of the placebo effect over the course of that task and (b) confirm that the placebo effect was intact and robust right before participants engaged in the picture-based task.

Preregistered analyses. As those manipulation checks, and thus the induction of a first-hand placebo analgesia effect, were deemed successful, we conducted our main analyses to test whether the first-hand effect of placebo analgesia transferred to picture-based empathy for pain. In general, we employed a within-subjects, full-factorial design with two factors of two levels each (target hand: left/control vs. right/placebo hand, intensity: pain vs. no pain). Two parametric two-factorial (2x2) repeated measures analyses of variance (ANOVAs) were used to analyze the results, where the dependent variables were either the pain or the unpleasantness ratings related to the viewing of the pictures. For each of the ANOVAs, we then compared the two hands on the index scores, separately for pain and unpleasantness ratings, using paired t-tests (always calculated as right/placebo hand (pain – no pain) < left/control hand (pain – no pain) and run one-tailed for $rating_{\text{right/placebo hand}} < rating_{\text{left/control hand}}$).

Post hoc analyses. As the pain rating data was not normally distributed (indicated by a significant Shapiro-Wilk normality test), we additionally calculated a Wilcoxon rank-sign test which mirrored the results of our parametric test (see section R.2 in the Supplement). Because of the (absence of predicted) behavioral results, we added two Bayesian paired-samples t-tests to evaluate evidence of absence of effects (Keysers et al., 2020). These analyses mirrored the preregistered behavioral analyses, using pain and unpleasantness ratings separately as dependent variables and the default Cauchy (0, .707) prior of .707 as the effect size (this indicates a 50% chance to observe an effect size between -.707 and .707; see

e.g., Rouder et al., 2009). In general, a Bayesian t-test generates one Bayes Factor that compares relative evidence for the alternative vs. null hypothesis (BF_{10}, H1 vs. H0; $BF_{10} \leq 3$: weak evidence, $BF_{10} > 3$: moderate evidence; $BF_{10} > 30$: strong evidence for H1) or the opposite, evidence for the null vs. the alternative hypothesis ($BF_{01} = 1/BF_{10}$; $BF01 \leq 3$: weak evidence, $BF_{01} > 3$: moderate evidence; $BF_{01} > 30$: strong evidence for H0) (Mac Giolla & Ly, 2019; Van Doorn et al., 2020; Wagenmakers et al., 2011). Bayesian analyses were run one-tailed for $rating_{right/placebo\ hand} < rating_{left/control\ hand}$ in JASP version 0.11.1 (JASP Team, 2019). The following section describes post hoc analyses we employed due to the null results found in the present study. As described below in the results, our present behavioral results showed no evidence for a placebo-induced decrease of subjective other-related pain or unpleasantness ratings related to the right/placebo hand. However, in another, previously published empathy task employing electrical stimulation conducted in the same participant sample and session, we did find evidence for a "generalized placebo effect", i.e., a general down-regulation of empathy for pain ratings in both left/control and right/placebo hand, independent of the localized placebo induction on only one hand (see also Supplement B of Hartmann, Rütgen, Riva, et al. 2021). In other words, the placebo manipulation had a general effect on the rating of our stimuli, independent of the target hand. Therefore, we wanted to investigate the existence of such a generalized downregulation by comparing behavioral ratings of the pictures used in our main study to the same pictures used in the validation study, where no placebo manipulation was employed. This was done by calculating two between-subjects ANOVAs, including either the pain or unpleasantness ratings in regard to the pictures, as well as the factors target hand (left/control vs. right/placebo hand), intensity (pain vs. no pain) and study (validation vs. main study). Effects indicating between-study differences were followed up using Welch's t-tests and evaluated two-sided. Note that none of these analyses were preregistered as they resulted from pattern of results and additional

insights and results originating between preregistration and data analysis and should thus be considered as exploratory.

fMRI data preprocessing and analysis

Preprocessing and first-level analysis. Statistical Parametric Mapping (SPM12, Wellcome Trust Centre for Neuroimaging, https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) running on MATLAB Version R2017b (Mathworks, 2018) was used for preprocessing and statistically analyzing the MRI data. Preprocessing involved slice timing (reference = middle slice; Sladky et al., 2011), realignment with each participant's individual field map, coregistration of structural and functional images, segmentation into gray matter, white matter (WM) and cerebrospinal fluid (CSF), spatial normalization, and spatial smoothing (8 mm full-width at half-maximum Gaussian kernel). The first-level design matrix of each participant contained four condition regressors and one for all ratings. For each condition, the onset and viewing duration (3.5 s) of the pictures were modeled as blocks and convolved with SPM12's standard canonical hemodynamic response function. Six realignment parameters and two regressors modeling WM and CSF were included as nuisance regressors (WM and CSF values were extracted using the REX toolbox by Duff et al., 2007).

Preregistered analyses. To test our hypothesis of a transfer of the first-hand localized placebo effect to empathy for everyday painful situations, we extracted and analyzed brain activation in three regions of interest (ROIs), determined independently from our data based on a meta-analysis on pain empathy (Lamm et al., 2011) and also used in our previous studies (Hartmann, Rütgen, Riva, et al., 2021; Rütgen, Seidel, Silani, et al., 2015): left AI (x = -40, y = 22, z = 0), right AI (39, 23, -4) and aMCC (-2, 23, 40). Additionally, we analyzed four ROIs in bilateral S1 (left S1: -39, -30, 51; right S1: 36, -36, 48) and S2 (left S2: -39, -15, 18; right S2: 39, -15, 18), taken from independent findings investigating somatosensory pain perception (Bingel et al., 2004, 2007). We created 10 mm spheres around each of the seven

coordinates with MarsBaR (Brett et al., 2002) and extracted parameter estimates for each ROI using the first-level contrast images of each participant and condition with REX (Response Exploration for Neuroimaging Datasets; Duff et al., 2007). ROI analyses were run in RStudio Version 3.6.1 (R Core Team, 2020). As in the behavioral analysis, we employed the same within-subjects, full-factorial design including two factors (*target hand*, *intensity*) of two levels each, and the additional factor *ROI* with seven levels (lAI, rAI, aMCC, lS1, rS1, lS2, rS2). We first calculated an ANOVA pooling the activation of all seven ROIs and then calculated separate ANOVAs and planned comparisons for each ROI. Each ANOVA was followed up by a planned comparison between the two hands using an index of the activation (pain -no pain). Since Mauchly's test for sphericity was statistically significant in the pooled ANOVA for the main effect of ROI and all interactions with the factor ROI, we reported the results of this ANOVA using Greenhouse Geisser sphericity correction. After observing a significant main effect of and interactions with the factor ROI in the initial three-way ANOVA, we went on with our preregistered plan and computed separate ANOVAs and planned comparisons for each ROI (one-sided tests for $\text{activity}_{\text{right/placebo hand}} < \text{activity}_{\text{left/control hand}}$). To control for multiple comparisons, we corrected the calculated *t*-tests using Bonferroni correction by dividing the α error probability by the number of ROIs (for tests in affective ROIs: $p = .05 / 3 \text{ ROIs} = .017$; somatosensory ROIs: $p = .05 / 4 \text{ ROIs} = .013$).

Post hoc analyses. Again, due to the (absence of predicted and exploratory evidence for opposite) results, we ran Bayesian paired-samples *t*-tests for each of the seven ROIs in JASP. The analyses of left and right S1 and S2 mirrored the preregistered fMRI analyses and were run one-sided for $\text{activity}_{\text{right/placebo hand}} < \text{activity}_{\text{left/control hand}}$ using the default Cauchy (0, .707) prior of .707 as the effect size. However, the analyses for the three affective ROIs (lAI, rAI and aMCC) were run one-sided for $\text{activity}_{\text{right/placebo hand}} > \text{activity}_{\text{left/control hand}}$ to investigate evidence for the opposite effect. Furthermore, we explored hand-related differences in other

regions apart from the ones preregistered by conducting an additional whole brain analysis for the contrasts $activity_{right/placebo\ hand} < activity_{left/control\ hand}$ and $activity_{left/control\ hand} < activity_{right/placebo\ hand}$, both calculated as pain – no pain (FWE-correcte at cluster level, k = 303).

3.3.4 Results

Behavioral results

Validation study. The aim of the validation study was to ensure that i) the stimuli for left and right hand did not differ and that ii) the stimuli in the pain and no pain conditions did differ from each other. We calculated five repeated measures ANOVAs for each of the five rating scales (pain, unpleasantness, realism, arousal, and valence) including the factors *target hand* (left vs. right hand) and *intensity* (pain vs. no pain). The results showed significant main effects of intensity in all ANOVAs (see Table 18 in the Supplement). Participants judged painful stimuli as significantly more painful ($F(1,37) = 538.24$, $p < .001$, $\eta^2 = 0.89$; Figure 15A in the Supplement) and unpleasant ($F(1,37) = 253.65$, $p < .001$, $\eta^2 = 0.75$; Figure 15B in the Supplement) as their non-painful counterparts. However, we did not find any significant differences in our measured variables between the two hands (main effect of target hand) or any interaction between intensity and target hand. These results successfully demonstrated the validity of our created task stimuli.

Manipulation checks. Next, we conducted two manipulation checks to evaluate the existence of a first-hand placebo analgesia effect. In the first check measuring beliefs in the effectiveness of the "medication" over the course of the session, means ± standard errors of the mean (*SEM*) were 6.64 ± 0.27 pre-conditioning, 8.06 ± 0.19 post-conditioning and 6.71 ± 0.39 post-session. The increase in effectiveness beliefs as a result of the conditioning procedure was significant (pre- vs. post-conditioning: $t(44) = 5.91$, $p < .001$, $M_{diff} = 1.42$, 95% $CI_{meandiff}$ [0.94, 1.91], see Figure 16A). Participants' beliefs dropped after the

completion of the task (post-conditioning vs. post-session: $t(44) = -3.80$, $p < .001$, $M_{diff} = -1.36$, 95% $CI_{meandiff}$ [-2.07, -0.64]), but did not drop lower than the initial effectiveness belief after gel application after the whole session (pre-conditioning vs. post-session: $t(44) = 0.16$, $p = 0.875$, $M_{diff} = 0.07$, 95% $CI_{meandiff}$ [-0.78, 0.92]). In the second check, we found a significant difference between the participant's placebo-treated vs. control-treated hands for first-hand pain ratings in the task preceding the picture-based task, with a very high effect size ($t(44) = 9.49$, $p < .001$ one-sided, $M_{diff} = 1.619$, 95% $CI_{meandiff}$ [1.28, 1.96], Cohen's $d_z = 1.42$; see Figure 16B). This difference was related to significantly lower pain ratings for the right hand ($M \pm SEM = 3.64 \pm 0.21$), i.e., the hand in which placebo analgesia was induced, compared to the left, control-treated hand ($M \pm SEM = 5.26 \pm 0.15$). Importantly, visual inspection of those first-hand pain ratings showed no sign of decrease over time and post hoc analysis of this time course also did not reveal any significant effects of trial number (p's > .281), suggesting a stable and robust placebo effect right before participants engaged in the picture-based task reported here. In sum, the two manipulation checks showed a) a strong belief in the effectiveness of the placebo gel that was highest right before entering the scanner, and b) lower subjective, first-hand pain ratings in a task that was done right before the picture-based empathy task we focus on here.

Preregistered analyses. Then, we went on to test our hypothesis and evaluate the existence of a transfer of the lateralized first-hand placebo analgesia effect to empathy for everyday painful situations in the main study. To this end, we calculated two repeated-measures ANOVAs (preregistered, see Table 19Table 20 in the Supplement). The first repeated-measures ANOVA using the pain ratings of the pictures revealed main effects of target hand ($F(1,44) = 5.42$, $p = .025$ two-sided) and intensity ($F(1,44) = 1348.88$, $p < .001$ two-sided), indicating that there were significantly higher pain ratings for the left/control vs. the right/placebo hand ($M_{right} \pm SEM = 3.02 \pm 0.30$; $M_{left} \pm SEM = 3.13 \pm 0.30$), and significantly

higher pain ratings for painful vs. non-painful pictures (M_{pain} ± SEM = 5.78 ± 0.09; M_{nopain} ± SEM = 0.37 ± 0.07; see Figure 11 for an overview of all ratings). However, we did not observe a target hand x intensity interaction (p = .711 two-sided), which would have shown evidence for pain-specific effects of the placebo manipulation. Paired comparisons mirrored those results, with no difference between the ratings (calculated as an index of painful - non-painful stimuli) of left/control (M ± SEM = 5.38 ± 0.17) and right/placebo (M ± SEM = 5.42 ± 0.14) hands (t(44) = -0.37, p = .823 one-sided, M_{diff} = -0.037, 95% $CI_{meandiff}$ [-0.24, 0.16], Cohen's d = 0.03).

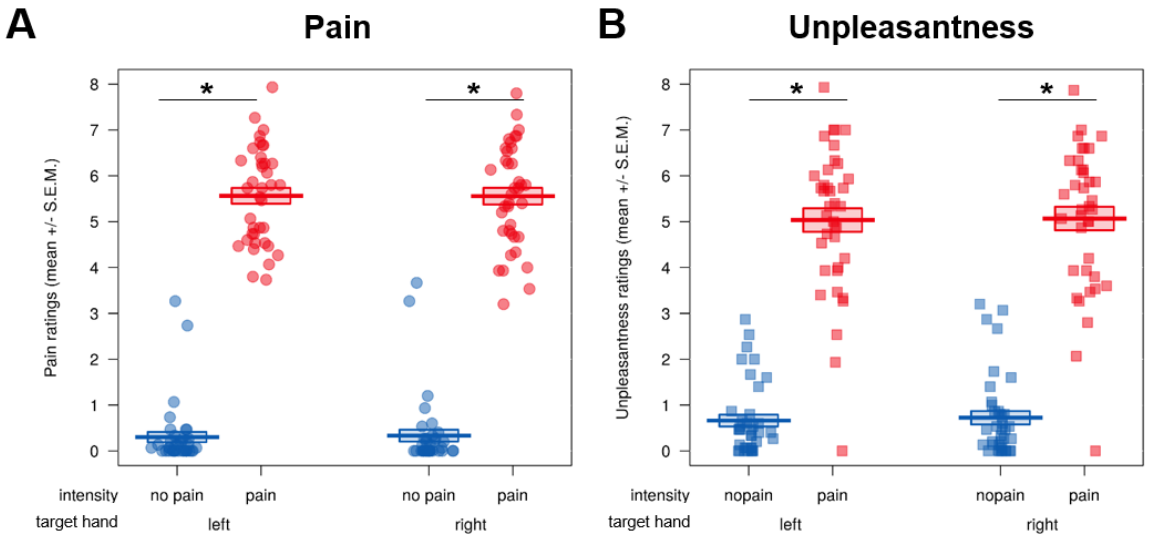

Figure 11. Preregistered behavioral results of the picture-based empathy for pain task, where participants rated pictures of others in painful and non-painful everyday situations (displayed here as an index of the ratings for painful – non-painful control stimuli). We observed no evidence for a transfer of the first-hand placebo effect induced using electrical pain to neither A) empathy for pain nor B) unpleasant-ness ratings, using a one-sided test of right/placebo hand < left/control hand. n.s. = not significant, S.E.M. = standard error of the mean; BF_{01} = evidence for the null compared to the alternative hypothesis (also calculated one-sided); ^{p} = preregistered. Figure taken from Hartmann, Riva, et al. (2021).

Results were similar in the second repeated-measures ANOVA using the unpleasantness ratings of the pictures. Here, we again observed main effects of target hand (F(1,44) = 15.56, p < .001 two-sided) and intensity (F(1,44) = 327.89, p < .001 two-sided), but opposite to the effect found in the pain ratings, there were significantly higher unpleasantness ratings for the right/placebo vs. the left/control hand (M_{right} ± SEM = 2.29 ± 0.23; M_{left} ± SEM = 2.14 ± 0.23), and significantly higher unpleasantness ratings for painful vs. non-painful pictures

($M_{pain} \pm SEM = 4.08 \pm 0.15$; $M_{nopain} \pm SEM = 0.35 \pm 0.07$). Again, we observed no target hand x intensity interaction ($p = .160$ two-sided), which would again have shown evidence for pain-specific effects. Paired comparisons (using an index of the ratings for painful – non-painful stimuli) showed no difference between the two hands (left: $M \pm SEM = 3.67 \pm 0.22$; right: 3.80 ± 0.21) for unpleasantness ratings ($t(44) = -1.43$, $p = .960$ one-sided, $M_{diff} = -0.13$, 95% $CI_{meandiff}$ [-0.32, 0.05], Cohen's $d = 0.09$).

Post hoc analyses. Complementing the above results, the two post hoc one-sided Bayesian *t*-tests showed moderate to strong evidence for absence of the investigated effect, both for pain ($BF_{01} = 8.07$) and unpleasantness ratings ($BF_{01} = 13.99$) of the main study. When comparing the main study's results to the one of the validation study (which had not included a placebo analgesia induction) in order to investigate a generalized effect of this manipulation in the main study, we observed main effects of target hand ($F(1,81) = 4.00$, $p < .048$ two-sided) and intensity ($F(1,81) = 1649.51$, $p < .001$ two-sided), but no main effect or interactions with study (for the full ANOVAs see Table 21Table 22 in the Supplement). The main effect of target hand showed that pictures of the right hand ($M \pm SEM = 3.04 \pm 0.22$) were rated as more painful than pictures of the left hand ($M \pm SEM = 2.98 \pm 0.22$) independent of the intensity or study, and that painful pictures ($M \pm SEM = 5.68 \pm 0.07$) were rated as more painful than non-painful pictures ($M \pm SEM = 0.35 \pm 0.06$) independent of the target hand or study. Looking at the unpleasantness ratings, however, we observed main effects of study ($F(1,81) = 11.37$, $p = .001$ two-sided), target hand ($F(1,81) = 11.78$, $p < .001$ two-sided) and intensity ($F(1,81) = 576.74$, $p < .001$ two-sided). Again, the main effect of target hand showed that pictures of the right hand ($M \pm SEM = 2.57 \pm 0.18$) were rated as more unpleasant than pictures of the left hand ($M \pm SEM = 2.46 \pm 0.18$) independent of the intensity or study, and that painful pictures ($M \pm SEM = 4.53 \pm 0.12$) were rated as more unpleasant than non-painful pictures ($M \pm SEM = 0.50 \pm 0.06$) independent of the target hand

or study. Interestingly, the main effect of study showed that, in general, pictures were rated as inducing more self-related unpleasant affect in the validation study ($M \pm SEM = 2.87 \pm 0.20$) compared to the main study ($M \pm SEM = 2.21 \pm 0.16$).

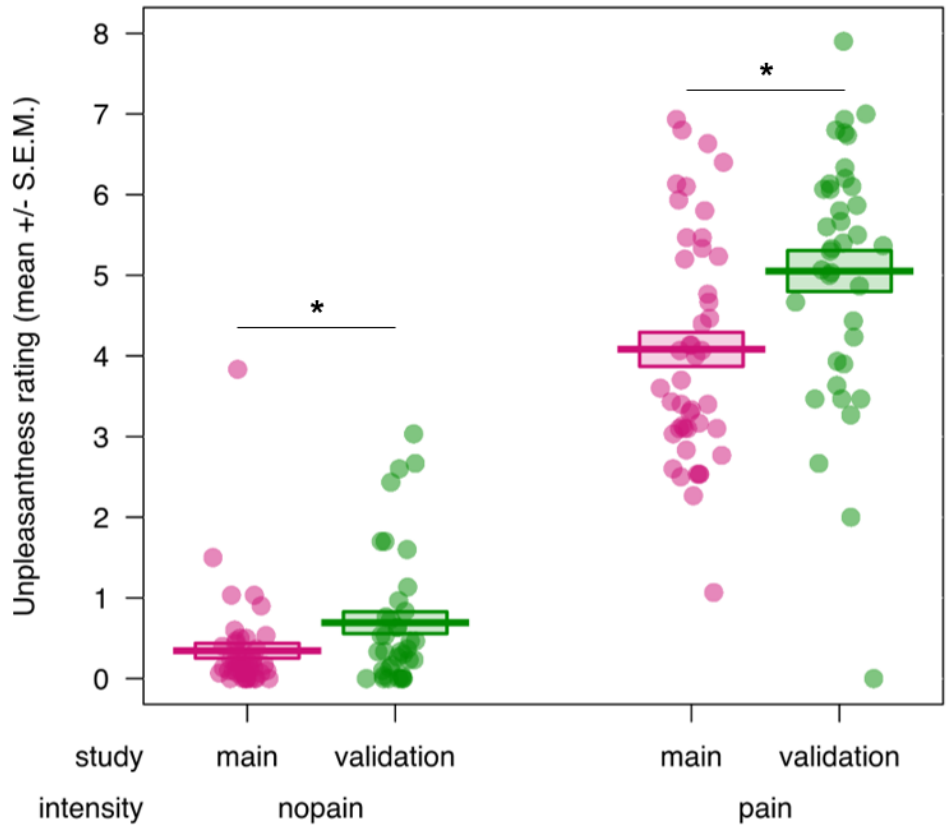

Figure 12. Post hoc comparison of unpleasantness rating to pictures of everyday painful situations between the validation and the main study (displayed here as an average of the ratings for stimuli depicting the right and left hand). We observed evidence for a significant, generalized reduction of unpleasantness in the main compared to the validation study, for pain as well as no pain stimuli. S.E.M. = standard error of the mean. Figure taken from Hartmann, Riva, et al. (2021).

We therefore followed up on the main effect of study by comparing the unpleasantness ratings for the two hands for the two studies, separately for pain and no pain (see Figure 12). Here we observed that, for both intensities, the average unpleasantness rating for either hand in the pictures was significantly higher in the validation compared to the main study (pain: $p = .004$, $M_{val} \pm SEM = 5.05 \pm 0.25$, $M_{main} \pm SEM = 4.08 \pm 0.21$; no pain: $p = .038$, $M_{val} \pm SEM = 0.69 \pm 0.14$, $M_{main} \pm SEM = 0.35 \pm 0.09$).

In sum, the behavioral results indicated no transfer of the placebo analgesia effect induced for first-hand electrical pain to empathy for pain or one's own unpleasantness during everyday situations. In other words, participants rated the pain intensity of other people in everyday situations as well as their own unpleasant affect when viewing such pictures equally high and independent of the placebo induction on the right hand. These results were confirmed by the post hoc Bayesian analyses. Interestingly, exploratory analyses indicated a possible down-regulatory effect of the placebo induction on unpleasantness ratings to the pictures in general, independent of the rated hand.

fMRI results

Preregistered analyses. After successfully inducing a first-hand placebo analgesia effect in our participants, we went on to test our preregistered main hypothesis for a transfer of this effect to empathy for everyday painful situations using a ROI approach. To this end, we extracted parameter estimates in three affective (bilateral AI, aMCC) and four somatosensory ROIs (bilateral S1 and S2). However, using our preregistered one-sided tests and hypothesizing a reduction of brain activation for pictures corresponding to the right/placebo hand, we did not find results confirming our hypotheses (see Table 17 for an overview of all planned comparisons). The pooled ANOVA showed significant main effects of intensity and ROI, a trend for target hand x intensity (p = .086 two-sided) as well as all interactions involving the factor ROI (see Table 23 in the Supplement for the full ANOVA table). The planned comparison encompassing activation of all ROIs revealed a non-significant result (p = .958 one-sided, M_{diff} = -0.08, 95% $CI_{meandiff}$ [-0.17, 0.01]), with no difference in activation for the right/placebo and the left/control hand. As preregistered, and due to a significant main effect of ROI as well as significant interactions with the factor ROI, we went on to calculate single ANOVAs and complementary t-tests for each ROI separately. Regarding the affective ROIs, we observed no evidence for lower placebo-induced hemodynamic activity in regard to

pictures displaying the right/placebo compared to the left/control hand (left AI: p = .995 one-sided, M_{diff} = -0.22, 95% $CI_{meandiff}$ [-0.37, -0.07]; right AI: p = .993 one-sided, M_{diff} = -0.18, 95% $CI_{meandiff}$ [-0.32, -0.04]; aMCC: p = .937 one-sided, M_{diff} = -0.14, 95% $CI_{meandiff}$ [-0.29, 0.01] also see Figure 13 here and Table 24Table *26* in the Supplement). However, the two-sided ANOVAs and visual data inspection revealed evidence for an opposite effect (a target x hand interaction showing increased activity for the right/placebo compared to the left/control hand (lAI: p = .005; rAI: p = .015; see Tables 38 and 39 in the Supplement), which we followed up on using post hoc Bayesian analyses.

Table 17

Main ROI analyses testing for placebo effects via one-sided paired t-tests.

Brain region	$M \pm SEM$		$t(44)^{p}$	$p_{one\text{-}sided}$	d_z
	left/control hand	right/placebo hand			
pooled ROIs	0.08 ± 0.04	0.16 ± 0.04	-1.76	.958	0.26
left AI	0.29 ± 0.07	0.50 ± 0.08	-2.99	.995	0.43
right AI	0.08 ± 0.06	0.26 ± 0.07	-2.54	.993	0.38
aMCC	0.22 ± 0.07	0.36 ± 0.08	-1.91	.937	0.28
left S1	0.05 ± 0.05	0.09 ± 0.06	-0.63	.733	0.09
right S1	-0.05 ± 0.05	-0.05 ± 0.06	-0.02	.506	< 0.01
left S2	0.005 ± 0.03	0.001 ± 0.02	0.15	.558	0.02
right S2	-0.03 ± 0.03	-0.05 ± 0.02	0.73	.766	0.11

Note. Planned comparisons for the region of interest (ROI) analyses to evaluate the transfer of a first-hand placebo analgesia effect to empathy for everyday painful situations. For bilateral AI and aMCC, we observed effects that were opposite to our preregistered predictions; p values for $activity_{right/placebo\ hand} < activity_{left/control\ hand}$ are displayed one-sided and interpreted using Bonferroni correction for multiple comparisons (p = .017 for affective ROIs and p = .013 for somatosensory ROIs); AI = anterior insula; aMCC = anterior midcingulate cortex; r/lS1 = right/left primary somatosensory cortex; r/l S2 = right/left secondary somatosensory cortex; M = mean; SEM = standard error of the mean; t(degrees of freedom); d_z = Cohen's d; ^{p} = preregistered.

In the somatosensory ROIs, we again found no evidence for our preregistered hypotheses, as there were no differences in brain activation for the two target hands, neither in S1 nor S2 (see Figure 14 and Table 27-Table *30* in the Supplement). More specifically, we did not

observe the hypothesized lower brain activity related to right/placebo hand compared to left/control hand pictures (left S1: $p = .733$ one-sided, $M_{diff} = -0.05$, 95% $CI_{meandiff}$ [-0.19, 0.10]; right S1: $p = .506$ one-sided, $M_{diff} < -0.001$, 95% $CI_{meandiff}$ [-0.13, 0.13]; left S2: $p = .558$ one-sided, $M_{diff} = 0.004$, 95% $CI_{meandiff}$ [-0.05, 0.06]; right S2: $p = .766$ one-sided, $M_{diff} = 0.02$, 95% $CI_{meandiff}$ [-0.04, 0.08]).

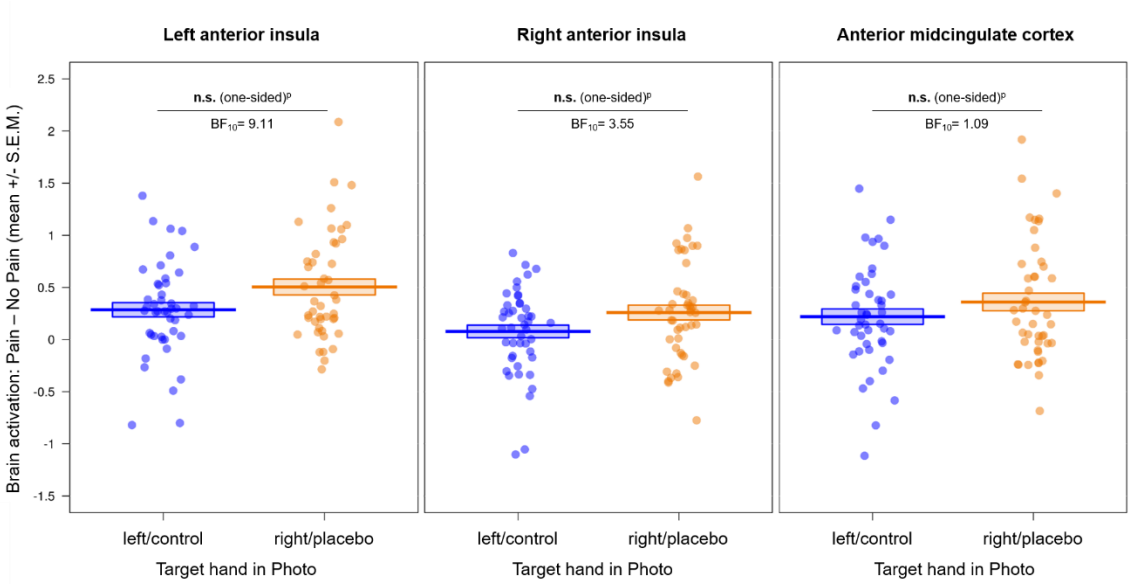

Figure 13. Affective region of interest (ROI) results of the empathy for pain task (displayed here as an index of activity related to painful – non-painful control stimuli). We observed no evidence for a reduction of brain activity in affective regions related to empathy for pain by the placebo manipulation, using a one-sided test of right/placebo hand < left/control hand. Data inspection revealed the opposite effect, i.e., higher activity in affective brain regions during empathy for pain in the placebo compared to the control condition. n.s. = not significant, S.E.M. = standard error of the mean; BF_{10} = evidence for the alternative compared to the null hypothesis; ᵖ = preregistered. Figure taken from Hartmann, Riva, et al. (2021).

Post hoc analyses. As mentioned above, inspection of the data revealed an opposite pattern in bilateral AI and aMCC, whereby activation seemed to be higher for right/placebo hand compared to left/control hand pictures. This was underlined by the significant target hand x intensity interactions observed for bilateral AI (and a trend for aMCC) in our preregistered ANOVAs. Post hoc Bayesian analyses of the seven ROIs can be found in Table 31 in the Supplement. Importantly, those only showed moderate evidence for H_1 compared to H_0 for lAI ($BF_{10} = 9.11$) and rAI ($BF_{10} = 3.55$), i.e., higher hemodynamic activity for right/placebo vs. left/control hand pictures, but weak evidence for H_1 in aMCC ($BF_{10} = 1.09$).

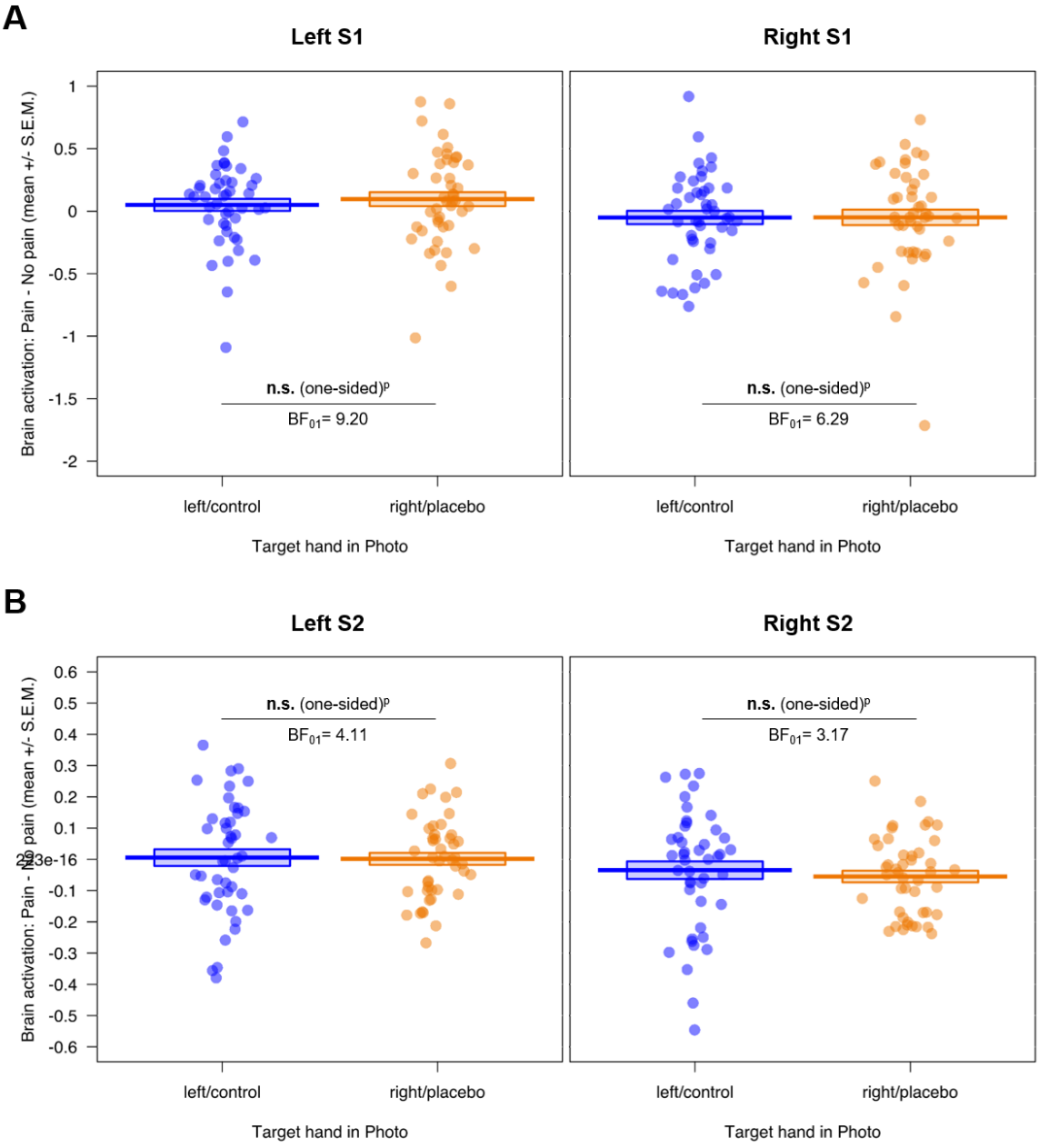

Figure 14. Somatosensory region of interest (ROI) results of the empathy for pain task for A) bilateral S1 and B) bilateral S2 (displayed here as an index of activity related to painful – non-painful control stimuli). We observed no evidence for a reduction of brain activity in somatosensory regions related to empathy for pain by the placebo manipulation, using a one-sided test of right/placebo hand < left/control hand. n.s. = not significant, S.E.M. = standard error of the mean; S1/S2 = primary/secondary somatosensory cortex; BF_{01} = evidence for the null compared to the alternative hypothesis; ^{p} = preregistered. Figure taken from Hartmann, Riva, et al. (2021).

In contrast, the Bayesian factors (BF_{01}) for the somatosensory ROIs showed moderate evidence for the absence of a difference in activity. The whole-brain analysis also did not reveal any evidence for other de- or increases in brain activity for right hand- compared to left hand-related stimuli, and vice versa. In sum, the results, similar to the behavioral results,

did not confirm our predictions of first-hand placebo analgesia reducing empathy for pain in both affective and somatosensory brain regions. However, exploratory post-hoc analyses suggested an opposite effect, i.e., higher hemodynamic activity related to right/placebo hand pictures in bilateral AI.

3.3.5 Discussion

This preregistered study aimed to investigate the role of sensory-discriminative brain responses in empathy for everyday painful situations. To this end, we induced a localized placebo analgesia effect in the right hand of 45 participants using a placebo gel (with the left hand acting as a control) and then measured brain activity with fMRI during an empathy for pain task focusing on visual depictions of painful situations occurring to left or right hands.

Contrary to our preregistered predictions, we did not observe a localized reduction of self-reported empathy for pain or unpleasantness ratings related to the hand laterality as a result of the first-hand placebo analgesia induction. The neuroimaging results mirrored the behavioral findings, as we did not observe evidence for lower hemodynamic activity in any of our affective or somatosensory ROIs as a result of the placebo. These null results were bolstered by three additional findings: First, pain and unpleasantness ratings in the validation study showed a reliable differentiation of painful vs. non-painful stimuli, but no differences on those dimensions for pictures displaying the left vs. right hand, speaking for the validity and comparability of our stimuli. Second, two initial manipulation checks showed an increase in the belief about medication effectiveness through the conditioning procedure, as well as a significant difference between first-hand pain ratings of the right/placebo and left/control hand in another task done in the same session (Hartmann, Rütgen, Riva, et al., 2021). Together, these results demonstrated the successful induction of a localized, first-hand placebo analgesia effect, thus laying a strong foundation to investigate their possible transfer to the picture-based empathy task. Third, Bayesian analyses using the behavioral and brain

data showed moderate to strong evidence for the absence of a transfer of lateralized placebo analgesia for first-hand pain to empathy for pain in our picture-based task. This suggests that shared somatosensory representations play less of a role during empathy for pain compared to shared affective representations, no matter how the pain of another person is inferred and where the attention of participants is directed. This interpretation is based on the observation that in two tasks both tailored to detect modulation of somatosensory sharing, we did not find evidence for modulation of such sharing by placebo analgesia. This contrasts with several previous studies that consistently reported modulation of processes and activity linked to affective representations (Rütgen, Seidel, Riečanský, et al., 2015; Rütgen, Seidel, Silani, et al., 2015; Rütgen et al., 2018, 2021).

Overall, our findings shed a different light on previous studies reporting an overlap of first-hand and empathy for pain in the sensory-discriminative component (Lamm et al., 2011 for a meta-analysis) and highlighting the role of somatosensory representations in empathy for pain (Avenanti et al., 2005; Bufalari et al., 2007; Riečanský & Lamm, 2019). However, it is important to note that unlike before, our study specifically targeted somatotopic matching of self- and other-related pain states by using a localized placebo manipulation targeted only at the right hand. One possible explanation for the here reported absence of somatosensory sharing could be that the general processing of another's pain might have a higher weight than processing the exact location and source of that pain, leading, in turn, to less involvement of the somatosensory network. Indeed, we cannot exclude a general down-regulation of somatosensory brain regions by placebo analgesia in the present study, as we did not have a between-subjects control group who was not under the influence of the placebo.

Our findings further tie in with studies investigating individuals with congenital insensitivity to pain (CIP), a patient group which is impaired in their first-hand and thus

somatosensory pain processing (Danziger et al., 2006, 2009). CIP patients still show intact empathic responses despite this constraint, including the aMCC and AI engagement seen in neurotypical controls, as well as ventromedial prefrontal and posterior cingulate cortices. Interestingly, those results were found using mainly measurements of empathy for pain focusing on pictorial displays or visual imagery (i.e., images of body parts and facial expressions, video material of painful situations, and verbally presented imaginary painful situations).

We further report exploratory evidence for generally lower unpleasantness as a result of the placebo analgesia induction in the main study, independent of the displayed hands (compared to our prior validation study without such analgesia). Averaging over both hands, we demonstrated significantly higher unpleasantness ratings in the validation study, compared to the main study. This indicates that the placebo induction might indeed have had an effect on the participants, but not in the localized way we expected. Instead, unpleasantness ratings were generally lower in the main compared to the validation study independent of the hand laterality in the stimuli. This finding would be in line with our past work (Rütgen, Seidel, Silani, et al., 2015) showing effects of a generalized placebo analgesia induction on affective brain networks, and with our previous study where we also observed such a general downregulation of empathic responses (Hartmann, Rütgen, Riva, et al., 2021). More specifically, there we had observed, within the same sample of participants, a comparable reduction of empathy for pain ratings for both hands instead of the expected localized reduction for the right hand only. These results underline the conclusion that the placebo analgesia induction in the present project, encompassing the present study and the one published in Hartmann, Rütgen, Riva, et al. (2021) may have influenced empathic resonance in a generalized, compared to a localized, way. Although this may not be too surprising, as the same subjects underwent this manipulation and did both tasks, it is

interesting to note that this general effect was observed consistently over both tasks and is in line with other work from our lab reporting evidence for affective shared representations (Rütgen, Seidel, Silani, et al., 2015). The absence of a localized transfer of the placebo effect raises the possibility of a domain-general affective blunting of empathy for pain responses in our study. However, we did not observe such a general blunting of responses during another task delivering first-hand electrical pain in the same session, where we saw a significant difference between the first-hand pain ratings of the two hands. Furthermore, a recent study from our lab (Rütgen et al., 2021) investigating exactly such domain-general effects showed that placebo analgesia does not transfer to pleasant touch, but only unpleasant touch and its empathic experience. In that study, only pain and empathy for pain, but not touch, were modulated by an opioidergic mechanism, which provided evidence for shared affective representations. Thus, it appears unlikely that our placebo induction procedure (which was very similar to the one in our previous studies, apart from employing placebo gel instead of pills) led to generally blunted affect but acted specifically on aspects related to the negative experience. Future studies should try to tease apart these specific vs. general effects more thoroughly.

In terms of advancing our theoretical understanding of empathy and its neural underpinnings, the present findings extend the insights of our previous studies, which had provided evidence for shared opioidergic mechanisms between pain and empathy for pain. With the present project, we refined the apparent limits regarding the level of specificity when it comes to sharing others' affective states. More specifically, it seems that we do not share others' pain representations in a body part-specific manner. What seems to be shared in empathy for pain are the affective consequences of the painful situation, rather than their precise bodily origins.

In addition, we observed a main effect of hand in our preregistered analysis, i.e., lower ratings for the right compared to left hand pictures independent of intensity, which could be another indication for a general placebo effect (especially as we did not observe this main effect in our validation study without any placebo induction). However, the actual difference in terms of rating was very small and previous between-subjects studies have reported an effect of the placebo only on pain (and not on no pain) ratings (Rütgen, Seidel, Riečanský, et al., 2015; Rütgen, Seidel, Silani, et al., 2015; Rütgen et al., 2018). Therefore, this reasoning about a general placebo effect is only preliminary and should be investigated further in future studies, especially because the validation and main study were not exactly the same: Apart from the 15 painful situations used in the validation and main study, the validation study employed a different set of participants, measured an additional 14 situations and also assessed realism, arousal and valence ratings for each picture. Although we chose the 15 most painful situations for the study comparison, the possibility of anchoring effects depending on the shown stimuli should be the subject of future research. In this context, an inherent limitation of our within-subjects design is the absence of a control condition for the placebo response, as all our participants underwent a placebo induction on their right hand. Although the validation study showed evidence for a generalized effect of the placebo, it can only supply indirect insights regarding the extent of placebo effects in the main study (see also Supplement B in Hartmann, Rütgen, Riva, et al., 2021 for a more thorough discussion of this issue). Future studies should aim for including such a condition in order to draw more conclusive conclusions about a possible general placebo effect and shared affective representations on the brain level.

Furthermore, we found an unexpected opposite effect for bilateral AI, whereby hemodynamic activity was higher for pictures of the right hand (corresponding to the participant's own placebo hand) compared to the left/control hand. It is important to note,

though, that these explorations were not part of our preregistered hypotheses and have to be interpreted with caution. Critically, we did not preregister an analysis testing for this unexpected finding of higher brain activity for pictures relating to the right/placebo as opposed to the left/control hand, as we hypothesized the opposite effect and thus tested one-sided. This caveat, coupled with our null findings and the nature of the picture-based task, which did not allow comparison to the first-hand experience of the corresponding situations, limit the conclusions we can make in regard to somatosensory sharing of another's pain. Although we report null results regarding our preregistered predictions, we briefly discuss our findings in the next section and highlight future research directions.

First, we induced the placebo only in the right hand of all our strongly right-handed participants, thus potentially confounding handedness with our placebo manipulation. It could therefore be that the right/placebo hand, always being the dominant hand, had specific effects on brain activation related to this hand, such as greater salience or attention. Indeed, Atlas and Wager (2014) discuss the possibility of placebo-induced changes in the insula and ACC changes reflecting attention or positive affective shifts. Future studies should therefore carefully test such laterality-related issues and extend this line of research, e.g., by counterbalancing the placebo analgesia induction and/or adding left-handers to their sample.

Second, previous research regarding first-hand as well as empathy for pain has also highlighted the role of stimulus context and appraisal mechanisms (Atlas et al., 2010; Hein & Singer, 2008 for a review; Lamm, Batson, et al., 2007; Lamm, Nusbaum, et al., 2007). For example, it has been shown that perspective changes can modulate evaluative processes and subsequent brain responses related to pain (Jackson, Brunet, et al., 2006), and that pain perception is shaped by multiple context factors such as expectations or beliefs (Jepma et al., 2018; Jepma & Wager, 2013). In our task, for example, the context varied greatly between the pictures and each situation had to be interpreted differently, possibly requiring increased

top-down perspective taking. In this line of reasoning, a failure of self-other distinction could have led to 'empathic over-arousal' in the form of higher brain activation in AI in the placebo compared to the control condition. However, to avoid confusion of self- and other-related perspectives, but also mixing up of the hand laterality, we purposefully chose to display the pictures from an egocentric perspective and kept a black frame around the images.

Third, we carefully selected placebo responders by means of four specific criteria (Hartmann, Rütgen, Riva, et al., 2021; Rütgen, Seidel, Silani, et al., 2015), i.e., only included participants showing a first-hand placebo analgesia effect. Wager et al. (2011) have highlighted a possibly altered process of pain evaluation in strong placebo responders, rather than a blockade of noxious input. Indeed, many previous studies not only find a decrease in pain-related brain regions but an additional increase in affective brain regions such as insula and rostral ACC for first-hand pain (Petrovic et al., 2002, 2005; Bingel et al., 2006), suggesting placebo-related modulatory mechanisms (also see Amanzio et al., 2013 and Atlas & Wager, 2014 for meta-analyses and placebo-related increases in other regions). If the pain is evaluated differently to begin with, this could explain our paradoxical increase of brain activity in bilateral AI, corresponding to processing of right-hand pictures. However, this is only speculative and should be thoroughly tested in future studies, especially since the evidence observed here was only moderate and the majority of studies using placebo analgesia usually report a decrease of activity in insular regions.

Two other important points are task order and time effects. Although we took great care in inducing the placebo effect in a way that it was stable for the whole session, the task reported here was conducted after another task, around 45 minutes after the placebo induction was completed. This could have influenced the strength of the placebo effect and led to a decrease or general change over time. However, both of our manipulation checks showed a persistent effect until the end of the session, visible in comparable beliefs in the effectiveness of the gel

from the start of the placebo induction to the end of the session, and in significantly lower (and stable) first-hand pain ratings for the right/placebo compared to the left/control hand in another task done right before the here presented empathy task. Furthermore, a previous study points to self-reinforcing expectancy effects in pain (Jepma et al., 2018). Indeed, the first-hand pain ratings in the placebo condition of the cue-based task completed directly before the picture-based task, showed no evidence for a decrease of the placebo effect over time.

As mentioned before, placebo analgesia in first-hand pain may not only have led to decreased brain activity in regions such as insula, ACC and S2, but also to increased activity in prefrontal regions such as dorsolateral, medial and orbitofrontal cortices as well as inferior frontal gyrus (see e.g., Atlas & Wager, 2014 for a meta-analysis). In line with this, neurons in the medial prefrontal areas might be involved in exerting placebo-related, modulatory control over an automatically triggered, affective response to the sight of highly aversive situations such as our stimuli (Lamm, Nusbaum, et al., 2007). However, a complementary, exploratory whole brain analysis did not reveal any activation differences for right/placebo vs. left/control hand in prefrontal areas in our task, when FWE-corrected at cluster-level. Investigating these brain regions in the context of analgesic effects on empathy for pain more specifically should therefore be the focus of future studies.

In conclusion, although our results suggest a successfully induced, localized placebo analgesia effect for first-hand pain, we did not find evidence for a somatotopically-specific reduction in brain activation, when assessing empathy for everyday painful situations. This study suggests that shared somatosensory representations play less of a role during empathy for pain compared to previously reported shared affective representations. Our work thus refines how empathy is processed in our brains, and the extent and type of influence that our first-hand pain experience has on empathic responding.

3.3.6 Funding

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3.3.8 CRediT author statement

Helena Hartmann: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Software, Visualization, Writing - original draft, Writing - review & editing. **Federica Riva**: Formal analysis, Supervision, Writing - original draft, Writing - review & editing. **Markus Rütgen**: Formal analysis, Methodology, Supervision, Writing - original draft, Writing - review & editing. **Claus Lamm**: Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing - original draft, Writing - review & editing.

3.3.9 Declarations of Interest

H. H. works as a researcher and psychologist for MyMind GmbH, a company developing a neurofeedback training game for children with Autism Spectrum Disorder, but this work is in no way related to the present research. The remaining authors declare that they have no financial interests or potential conflicts of interest.

3.3.10 Supplement

This study is part of a bigger project that has in part already been published, with the only difference being the task that was reported (Hartmann, Rütgen, Riva, et al., 2021). Most of the information given here in M.1, M.2, M.3 and M.5 is therefore paraphrased from this previous paper.

Methods

M.1 Sample. Participants were recruited via a database of interested study participants, distributing flyers and advertising on social media. Interested participants first filled out an online questionnaire screening for any exclusion criteria (especially regarding MRI safety) and only eligible participants were invited to the study. Exclusion criteria were past/present enrollment in university studies including psychology, pharmaceutics or (human, veterinary, dental, etc.) medicine, any psychiatric or neurological conditions, past/present long term self-injurious behavior, past or present medical conditions regarding the hands that could possibly interfere with current pain sensitivity (e.g. chronic pain, numbness, trauma, injuries or long-term pain therapy), past/present alcohol or drug abuse, the intake of psychopharmacological medication in the last three months (besides oral contraceptives), left-handedness or no handedness preference, and a weakness in distinguishing left from right. The latter was operationalized by asking participants how often they mix up left and right in their daily life, e.g., while making a turn with the car. We excluded participants answering this question with 'sometimes', 'often' or 'always'. Handedness was measured using a combination of two established handedness questionnaires (Oldfield, 1971; Büsch et al., 2009). A laterality quotient (LQ; going from -100 = strongly left-handed to +100 = strongly right-handed) was calculated from the ten most selective items of the two questionnaires, and only individuals with LQs ≥ 72 were invited to the take part (Tran et al., 2014). Each participant was tested twice for any contraindications regarding MRI scanning, once via an online screening

questionnaire and once in person at the outset of the scanning session. Excluded participants, such as dropouts and placebo analgesia nonresponders (see also next section S.2), were replaced until the preregistered sample size of 45 participants was reached.

M.2 Nonresponder identification. Placebo analgesia nonresponders were determined using four exclusion criteria (the first three criteria taken from (Rütgen, Seidel, Silani, et al., 2015): (1) We recorded any strong, verbally expressed doubts regarding the study setup during and after the session; (2) We collected belief scores about the effectiveness of the gel to decrease the participant's own pain at three time-points during the session (after the gel application = pre-conditioning, after the conditioning = post-conditioning, and in the post-experimental questionnaire = post-session, each rating on a continuous visual-analogue-scale from 0-10 cm). Pre- and post-conditioning ratings that were < 6.66 cm in sum (indicating a general low belief) and/or pre- minus post-conditioning ratings that were > 3.33 cm (indicating a decrease in belief after the conditioning) classified a participant as a nonresponder. (3) We counted the number of conditioning trials needed to show an analgesic response, with four or more trials indicating nonresponding. However, none of the participants needed more than three conditioning trials to show a response to the placebo; (4) During the data collection, we preregistered a fourth measure we had previously overlooked, as it had not been possible in the previous study (which mainly informed the pre-registration) due to a between-subjects design. This involved a first-hand pain task, where we applied short-lasting painful and non-painful electrical stimulation delivered to the right/placebo and left/control hands of the participant, and then collected pain ratings (for a more thorough report see also Hartmann, Rütgen, Riva, et al. 2021). Using this fourth criterion, we could directly compare the self-related pain ratings of the two hands and excluded participants who showed higher average first-hand pain on the right/placebo compared to the left/control hand. This allowed us to identify responders with increased certainty, and thus maximize the placebo responsiveness

of the sample as well as bolster interpretability of our results. During preregistration of this addendum, the so far collected data had not been observed or analyzed yet.

M.3 Procedure. In brief, the study consisted of two parts: First, participants were invited to an initial one-hour session to the Faculty of Psychology and were asked to fill out different trait personality questionnaires on a computer for around one hour. For the second session (average interval of 32.86 ± 29.16 (*M* ± *SD*) days), participants were asked to refrain from alcohol, drugs, or medication-intake 24 hours before the testing session as well as from intake of food or any other drink besides water one hour before. In general, participants were asked to rate each stimulation as intuitively but also as accurately as possible. We calibrated the left and right hand individually for each participant (alternating the hand being calibrated first across participants), because previous studies found pain tolerances to vary depending on the hand laterality and dominance (Murray & Safferstone, 1970; Pud et al., 2009). For the placebo induction, a combination of verbal suggestions and classical conditioning techniques was employed. First, a medical student posing as the study doctor (either male or female) did a brief medical screening including a (pseudo) drug-test to increase participant's belief in the cover story that a real medication would be administered. The placebo gel was presented as a "potent, local anesthetic" with pain-reducing effects on the part of the skin where it is applied to for around 2-3 hours and that its maximum effectiveness would thus last the whole scanning time. Importantly, participants were told that the medical gel blocked pain receptors in a pharmacological way and would thus exert no effects on normal touch sensitivity or non-painful stimulation intensity. This was done to ensure a belief decrease due to an absence of possibly expected skin numbing. In addition, the "medication" was described as already being well established since many years, legally approved, and routinely used in e.g., dental procedures and chronic pain patients. Participants were told that possible side effects in very rare cases could be dry skin and slight skin irritation. The placebo gel was always applied

first on the dorsum of the right hand and directly after that the control gel on the left hand, which was described as a normal basic skin cream and representing a basis for the participant's typical pain perception (the word "placebo" was never mentioned to the participants over the course of the experiment). Participants were told that the application of different gels on each hand was routinely done to ensure equal conditions and make them comparable for later analysis. Both the placebo and control gel contained 0.5 g Carbomer, 0.09 g TRIS, 15 g undiluted Isopropanol, 10 g Propylenglykol, 3 g Glycerol and Aqua pur. ad 100 g, the only difference being 10 g (out of 100 g) Isopropanol in the placebo gel and 10 g basic skin cream ('Ultrasicc') instead of the Isopropanol in the control gel. This difference led to a clearly recognizable visual and olfactory distinction between the gels, while still keeping them matched with regard to tactile feeling and hydrating properties. Here we adhered to previously used procedures inducing placebo analgesia by means of topical creams and gels (Benedetti et al., 1999; Bingel et al., 2006; Geuter et al., 2013; Schenk et al., 2014). After the gel application on both hands, the participant was led outside the control room to (ostensibly) wait for the medication to take effect and received detailed instructions regarding the task. Then we asked participants back in the control room and told them that a "pain test" would be used to check the effectiveness of the medication. Before the conditioning and application of new electrodes in the same location as during calibration, excess gel was removed, and the hands were disinfected with 70% isopropyl rubbing alcohol. A conditioning round was deemed successful, if all stimuli on the right/placebo hand were rated with lower than 6 and all stimuli on the left/control hand higher than 5. After unsuccessful rounds, stimulation intensity was slightly adjusted, i.e., increased for the left/control hand and/or decreased for the right/placebo hand, in order to increase the contrast between the hands. In the first conditioning round three stimulations were administered, in subsequent rounds four.

M.4 Picture-based empathy for pain task. The pictures were taken with a Canon EOS 1100D Camera (ISO 6400, 12.2 Megapixel) from an egocentric perspective to facilitate "putting oneself in the shoes of the other", as no mental rotation of the hand position was required of the participants. As in the study by Jackson and colleagues (Jackson et al., 2005), all situations depicted events happening in everyday life, such as jamming the hand in a cupboard or burning your hand in the oven and used different types of pain (mechanical, thermal and pressure). Minor clean-up, image improvements and insertion of black arrows were done with Adobe Photoshop CS3. All pictures were rescaled to 700x525 pixels for the task and displayed on a BOLD screen 32 LCD for fMRI (https://www.crsltd.com/tools-for-functional-imaging/mr-safe-displays/boldscreen-32-lcd-for-fmri/nest/boldscreen-32-technical-specification#npm) which participants watched through a mirror mounted on the head coil. The hand participants rated with was counterbalanced between but kept constant within participants over all tasks in order to avoid any effects in the right/placebo hand being related to hemodynamic activity during rating. In the validation study, we additionally asked participants to judge the realism ("Can you imagine this happening to you in real life?") on a 9-point visual analogue scale from 0 = "not at all" to 8 = "extremely realistic", as well as arousal and valence of each picture (via 9-point Self-Assessment Manikins (SAM) from "calming" to "exciting" (arousal) and from "negative" to "positive" (valence); see e.g. Bynion and Feldner 2017).

M.5 Data analysis and plotting. The following packages (functions) were used for analyses and plotting in RStudio: plyr (ddply), dplyr (arrange), stats (shapiro.test, t.test, cor.test, aggregate), tidyr (gather, spread), reshape2 (dcast), ez (ezANOVA), yarrr (pirateplot) and ggplot2 (ggplot). All Figures were created in Microsoft PowerPoint.

Results

R.1 Validation study. In Table 18 and Figure 15, we report the ANOVA results of the validation study. Non-painful stimuli were rated as significantly more calming ($F(1,37) = 130.97$, $p < .001$, $\eta^2 = 0.53$) and positive ($F(1,37) = 109.92$, $p < .001$, $\eta^2 = 0.66$) than painful stimuli. Although stimuli were judged as realistic in general, painful stimuli were rated as significantly less realistic as non-painful stimuli ($F(1,37) = 83.77$, $p < .001$, $\eta^2 = 0.33$). Importantly, although the validation study showed that stimuli were judged as realistic in general, painful stimuli were rated as significantly less realistic than non-painful stimuli. This is no surprise, as we asked how realistic participants imagine that the situations happen to them in everyday life and non-painful situations occur more often. Crucially, we did not find any significant differences in pain, unpleasantness, realism, arousal, or valence between pictures focusing on the right or left hand, showing that any possible differences in realism affected the processing of pictures related to either hand in a similar way.

Table 18
Behavioral results of the ANOVAs in the validation study.

Tests and effects	$F_{(1,37)}$	$p_{(two\text{-}tailed)}$	*gen.* η^2
Pain			
target hand	0.12	.736	< 0.001
intensity	538.24	< .001	0.89
target hand x intensity	0.41	.524	0.001
Unpleasantness			
target hand	1.21	.278	0.004
intensity	253.65	< .001	0.75
target hand x intensity	0.15	.701	< 0.001
Arousal			
target hand	0.54	.466	< 0.001
intensity	130.97	< .001	0.53
target hand x intensity	1.59	.215	0.001
Valence			
target hand	2.28	.139	< 0.001
intensity	109.92	< .001	0.66
target hand x intensity	1.55	.221	< 0.001
Realism			

target hand	1.99	.166	< 0.001
intensity	83.77	< .001	0.33
target hand x intensity	0.49	.490	< 0.001

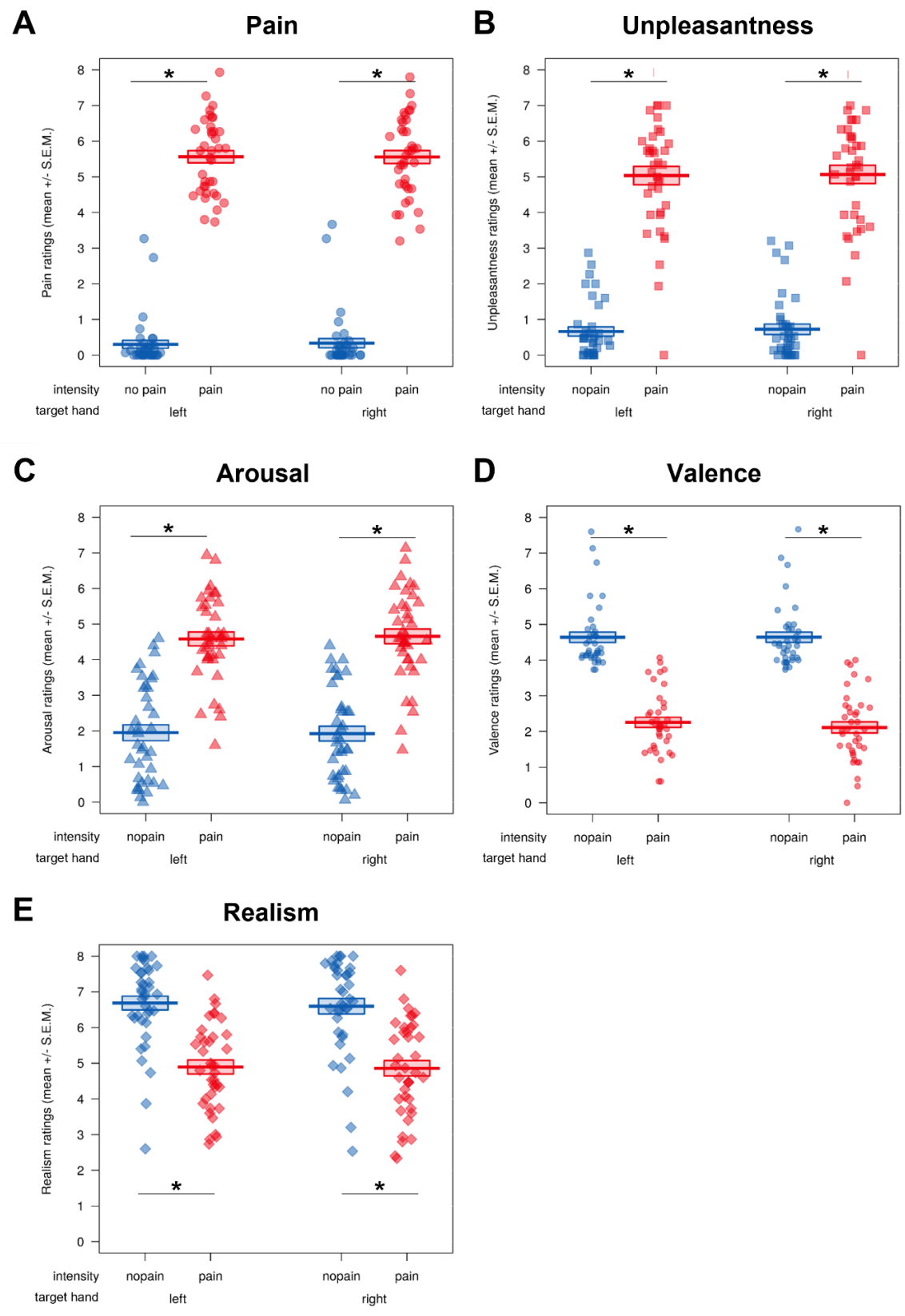

Figure 15. Behavioral results of the validation study. Participants rated picture stimuli of everyday painful and non-painful situations, separately for the left and right hand, and according to the following dimensions, all on 9-point Likert scales: A) pain (0 = "not at all" to 8 = "extremely painful"), B) unpleasantness (0 = "not at all" to 8 = "extremely unpleasant"). Apart from pain and unpleasantness, participants rated pictures of everyday painful/non-painful situations on three additional dimensions, separately for the left and right hand, all on 9-point Likert scales: C) arousal (0 = "calming" to 8 = "exciting"), D) valence (0 = "negative" to 8 = "positive") and E) realism (0 = "not at all" to 8 = "extremely realistic"). In all 2x2 ANOVAs using the factors target hand (left vs. right) and intensity (pain vs. no pain), we observed significant main effects of intensity, demonstrating that painful stimuli were rated as significantly more painful, more unpleasant, less realistic, more arousing, and more negative than their non-painful counterparts. We found no significant differences in our variables between the two hands (main effect of target hand) or any interaction between intensity and target hand. The validation study was not preregistered but conducted before (the preregistration of) the main study. Figure taken from Hartmann, Riva, et al. (2021).

R.2 Manipulation checks. Here we report a figure of the manipulation check data, belief ratings about the effectiveness of the "medication" over the course of the session (Figure 16A) and first-hand electrical pain ratings in the task preceding the picture-based task (Figure 16B).

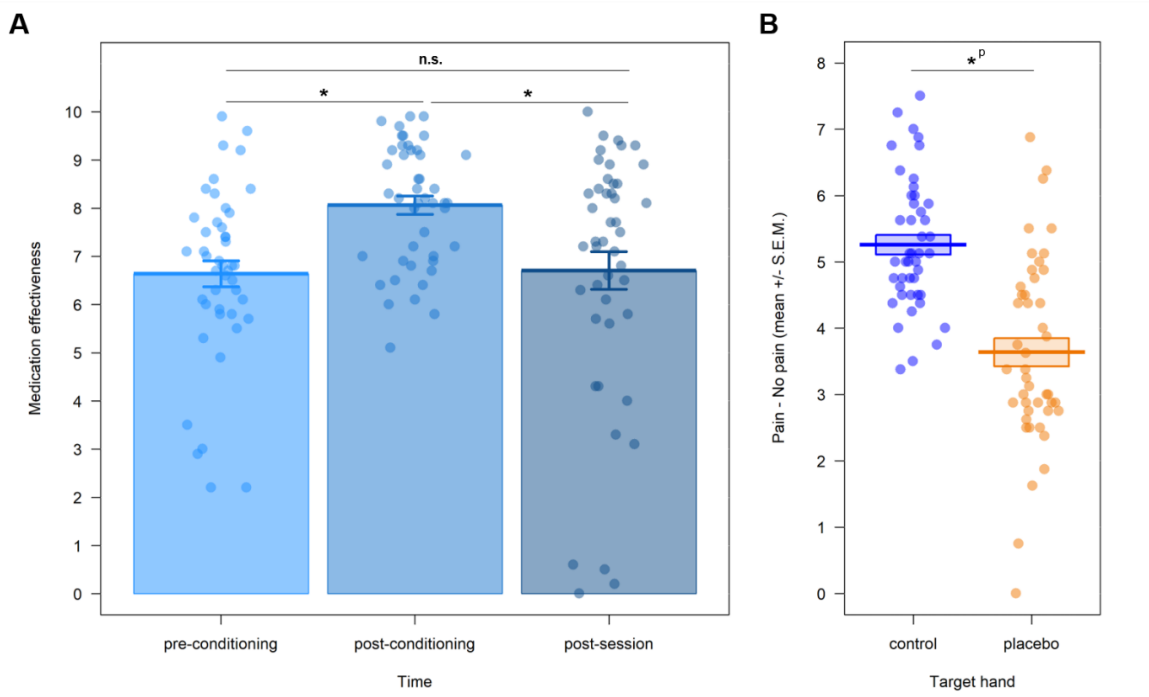

Figure 16. Behavioral manipulation checks to evaluate the strength of the first-hand placebo effect. Displayed are means and standard errors of the mean. A) We evaluated beliefs in the effectiveness of the administered gel at three times during the experiment - directly after the application by the medical cover (pre-conditioning), after the conditioning procedure (post-conditioning) and during the debriefing at the end of the session (post-session). This revealed a significant increase of beliefs after the conditioning. Although the beliefs significantly decreased until the end of the session, they did not drop significantly lower than initial belief levels, which were already high to begin with. B) We further evaluated first-hand pain ratings from another task done in the same session where individually calibrated, painful and non-painful electrical stimulation was delivered to the right and left dorsum of participant's hands (for a thorough description of

this task, see Hartmann, Rütgen, Riva, et al., 2021); displayed here as an index of the ratings for painful – non-painful stimulation). Here we observed a significant placebo analgesia effect. * $p < .05$; S.E.M. = standard error of the mean; [p] = preregistered. Figure taken from Hartmann, Riva, et al. (2021).

R.3 Main behavioral analyses. Because the assumption of normality was violated for the pain rating data in the main study, we additionally calculated a Wilcoxon rank-sign test using the pain ratings. Similar to the preregistered ANOVA and *t*-test above, this did not reveal a statistically significant difference in pain ratings between the two hands ($p = .293$ one-tailed, Cohen's $d = 0.03$). Below we report the full ANOVA tables (Tables 19 and 20) of behavioral results of the main study.

Table 19
Behavioral results of the ANOVA using pain ratings.

Effects	$F_{(1,44)}$	$p_{(two\text{-}tailed)}$	*gen.* η^2
target hand	5.42	.025	0.004
intensity	1348.88	< .001	0.93
target hand x intensity	0.14	.711	< 0.001

Table 20
Behavioral results of the ANOVA using unpleasantness ratings.

Effects	$F_{(1,44)}$	$p_{(two\text{-}tailed)}$	*gen.* η^2
target hand	15.56	< .001	0.004
intensity	327.89	< .001	0.74
target hand x intensity	2.04	.160	< 0.001

R.4 Study comparison. Here we report the full ANOVA tables of the exploratory comparison of pain and unpleasantness ratings between the validation and the main study (Tables 21 and 22).

Table 21
Behavioral results of the study comparison ANOVA using pain ratings.

Effects	$F_{(1,81)}$	$p_{(two\text{-}tailed)}$	*gen.* η^2
study	1.19	.277	0.01
target hand	4.00	.049	0.001
intensity	1649.51	< .001	0.91
study x target hand	2.57	.113	< 0.001
study x intensity	0.36	.545	0.002
target hand x intensity	< 0.001	.978	< 0.001
study x target hand x intensity	0.39	.528	< 0.001

Table 22
Behavioral results of the study comparison ANOVA using unpleasantness ratings.

Effects	$F_{(1,81)}$	$p_{(two\text{-}tailed)}$	gen. η^2
study	11.37	.001	0.73
target hand	11.78	< .001	0.002
intensity	576.74	< .001	0.75
study x target hand	3.09	.083	< 0.001
study x intensity	3.42	.068	0.02
target hand x intensity	0.75	.329	< 0.001
study x target hand x intensity	1.77	.188	< 0.001

R.5 Region of interest analyses. Below we report the full ANOVA tables of the fMRI results (pooled activation of all ROIs in Table 23 and single ANOVAs for each ROI in Tables 24- 30) as well as the post hoc Bayesian analyses (Table 31).

Table 23
ANOVA using pooled activation of seven ROIs.

Effects	*df*	*F*	$p_{(two\text{-}tailed)}$	gen. η^2
target hand	1,44	0.16	.689	< .001
intensity	1,44	13.21	< .001	0.016
roi^S	6,264	20.50	< .001	0.144
target hand x intensity	1,44	3.09	.086	0.002
target hand x roi^S	6,264	3.35	.003	0.002
intensity x roi^S	6,264	20.19	< .001	0.028
target hand x intensity x roi^S	6,264	4.61	< .001	0.002

Note. Effects marked with an "S" had a significant Mauchly's test for sphericity and corresponding *p*-values are reported using Greenhouse Geisser sphericity correction. The following regions of interest were included: l/rAI = left/right anterior insula, aMCC = anterior midcingulate cortex, l/rS1 = left/right primary somatosensory cortex, l/rS2 = left/right secondary somatosensory cortex.

Table 24
ANOVA of left anterior insula.

Effects	$F_{(1,44)}$	$p_{(two\text{-}tailed)}$	gen. η^2
target hand	1.21	.278	0.002
intensity	39.98	< .001	0.162
target hand x intensity	8.93	.005	0.015

Table 25
ANOVA of right anterior insula.

Effects	$F_{(1,44)}$	$p_{(two\text{-}tailed)}$	*gen.* η^2
target hand	0.42	.521	< .001
intensity	9.09	.004	0.040
target hand x intensity	6.47	.015	0.012

Table 26
ANOVA of anterior midcingulate cortex.

Effects	$F_{(1,44)}$	$p_{(two\text{-}tailed)}$	*gen.* η^2
target hand	0.23	.636	< 0.001
intensity	16.88	< .001	0.053
target hand x intensity	3.64	.063	0.003

Table 27
ANOVA of left primary somatosensory cortex.

Effects	$F_{(1,44)}$	$p_{(two\text{-}tailed)}$	*gen.* η^2
target hand	0.03	.862	< 0.001
intensity	3.85	.056	0.003
target hand x intensity	0.39	.534	< 0.001

Table 28
ANOVA of right primary somatosensory cortex.

Effects	$F_{(1,44)}$	$p_{(two\text{-}tailed)}$	*gen.* η^2
target hand	7.59	.008	0.007
intensity	1.10	.300	0.002
target hand x intensity	< 0.001	.988	< 0.001

Table 29
ANOVA of left secondary somatosensory cortex.

Effects	$F_{(1,44)}$	$p_{(two\text{-}tailed)}$	*gen.* η^2
target hand	0.26	.614	< 0.001
intensity	0.03	.853	< 0.001
target hand x intensity	0.21	.885	< 0.001

Table 30
ANOVA of right secondary somatosensory cortex.

Effects	$F_{(1,44)}$	$p_{(two\text{-}tailed)}$	*gen.* η^2
target hand	4.00	.052	0.005
intensity	5.29	.026	0.010
target hand x intensity	0.54	.468	< 0.001

Table 31
Overview of the results in the Bayesian t-tests for the seven ROIs.

Region of interest	MNI coordinates	Prior	BF_{01}	BF_{10}
aMCC	-2 23 40	Cauchy (0, .707)	0.92	1.09
lAI	-40 22 0	Cauchy (0, .707)	0.11	9.11
rAI	39 23 -4	Cauchy (0, .707)	0.28	3.55
lS1	-39 -30 51	Cauchy (0, .707)	9.20	0.11
rS1	36 -36 48	Cauchy (0, .707)	6.29	0.16
lS2	-39 -15 18	Cauchy (0, .707)	4.11	0.24
rS2	39 -15 18	Cauchy (0, .707)	3.17	0.32

Note. MNI coordinates are given as x, y, and z; AI = anterior insula; aMCC = anterior midcingulate cortex; r/lS1 = right/left primary somatosensory cortex; r/l S2 = right/left secondary somatosensory cortex; BF_{01} = Bayes Factor evidence for null hypothesis (H_0 vs. H_1); BF_{10} = Bayes Factor evidence for alternative hypothesis (H_1 vs. H_0); $BF_{10} = 1/BF_{01}$. Bayesian *t*-tests were run in JASP, one-sided for $activity_{right/placebo\ hand} > activity_{left/control\ hand}$ (lAI, rAI, aMCC) or $activity_{right/placebo\ hand} < activity_{left/control\ hand}$ (lS1, rS1, lS2, rS2).

4 Another's Pain in my Social Brain

"We have a responsibility to help those
around us and help others in need."
– Virginia Williams –

4.1 Preregistration of Study 3

The main preregistration can be found on the Open Science Framework (https://osf.io/g3acp), while a brief addendum was uploaded later (https://osf.io/qw3kg).

Study Information

Title

The effects of placebo (empathy) analgesia on prosocial behavior.

Description

Previous results regarding placebo analgesia showed that a down-regulation of first-hand pain by means of a placebo pill presented as a painkiller influences the way we empathize with another person in pain (Rütgen, Seidel, Riečanský, et al., 2015; Rütgen, Seidel, Silani, et al., 2015). More concretely, this was shown on a behavioral level by significantly reduced subjective pain ratings related to one's own and another's pain as well as on a neural level by decreased activity in specific brain areas (anterior insula, anterior midcingulate cortex) in the placebo group compared to a control group who received no pill.

However, although empathy and prosocial behavior are closely linked and positively correlated (e.g. Brethel-Haurwitz et al., 2018; Eisenberg & Miller, 1987; Lamm & Tomova, 2018; Lockwood et al., 2016; Singer & Lamm, 2009; Tomova et al., 2017) effects of placebo analgesia on prosocial behavior towards others (as opposed to subjective affective judgements of another's pain) have not been tested as of yet. In other words, it is still not clear if the first-hand pain- and unpleasantness reduction and the subsequent reduction of

empathic pain perception, induced by first-hand placebo analgesia, have an influence on moral social behavior that we show towards others (operationalized here by exerting actual physical effort to lower another person's pain; see also Crockett et al., 2015; Lockwood, Hamonet, et al., 2017). Therefore, the main objective of the present project is to answer the following research question: Do placebo analgesics also have effects on prosocial behaviors, being related to their previously documented changes of social emotions? More concretely, does induction of placebo analgesia modulate the amount of prosocial behavior individuals show towards others in a pain avoidance context, and if so, in what direction?

Hypotheses

1. Placebo analgesia leads to lowered empathic responses (directional hypothesis, manipulation check).
2. Consequently, we expect an effect of the lowered empathic response on prosocial behavior.

    2a. Reduced prosocial behavior. If participants' empathy is downregulated by the placebo, participants in the placebo group would show less prosocial behavior due to their decreased empathic sharing of another's pain (we would predict this direction with the most confidence). Participants with placebo analgesia will exhibit a decreased willingness to choose an effortful option to lessen another's pain and/or show a decreased amount of actual force exerted.

    2b. Increased prosocial behavior. However, the reduced first-hand pain by means of the placebo could also lead to higher prosociality in the placebo group, because the general reduction of unpleasantness leads to a greater tolerance (i.e., less aversiveness) of effort in general. Participants with placebo analgesia will exhibit increased willingness to choose an effortful option to lessen another's pain and/or in an increased amount of actual force exerted.

2c. No effect on prosocial behavior. Finally, it could be that placebo analgesia influences affective sharing but does not transfer to social behavior, leading to no difference between placebo and control group. Participants with and without placebo analgesia would then exhibit a similar willingness to choose an effortful option to lessen another's pain and/or show an equal amount of actual force exerted in both groups.

3. This could have multiple reasons that we want to further elaborate here:

3a. The effect of the placebo on empathy was not strong enough to further influence prosocial behavior. In this case we would expect an effect size smaller than the ones found in previous studies (Rütgen, Seidel, Riečanský, et al., 2015; Rütgen, Seidel, Silani, et al., 2015).

3b. The effect of the placebo on empathy was strong enough (measured by comparing the effect sizes as in 3a), but this does not affect prosocial behavior. In that case we would investigate the association between reduced empathy in the manipulation check and prosocial behavior in the main task, with a weaker correlation pointing to less association of empathy and prosocial behavior in our experiment.

3c. True null effect.

Design Plan

Study type

Experiment - A researcher randomly assigns treatments to study subjects, this includes field or lab experiments. This is also known as an intervention experiment and includes randomized controlled trials.

Blinding

No blinding is involved in this study.

Is there any additional blinding in this study?

None.

Study design

The study employs an experimental, full-factorial, mixed design with two tasks. The pain task uses 3 factors (between-subject variable = treatment (placebo, control), within-subject variables = intensity (pain, no pain), target (self, other)). The prosocial effort task uses 3 factors (between-subject variable = treatment (placebo, control), within-subject variables = effort (5 levels), helping (5 levels)). See below for a thorough description of the variable levels.

Randomization

Participants will be pseudorandomly allocated to either the placebo or control group which will act as a between-subjects factor. A document with subject codes and group allocation will be created beforehand, where placebo and control sessions are alternated (Example: Subject_01 = CTR, Subject_02 = PLA, Subject_03 = CTR, etc.). Dropouts in each group will be replaced and added at the end of this document until the final group sizes are reached. We will aim at an equal (50:50) sex distribution in each group.

Trials of the pain task will be shown in a pseudorandomized order (four sequences will be created manually for each task and alternated over all participants in an a-priori defined order, however, the pain training will involve only other-related electrical stimulation and the pain task will start with four non-random other-related stimuli and be followed by the rest of the conditions in the previously specified pseudorandom order). Blocks of the prosocial effort task will be pseudorandomized, but trials within a block will be kept constant over all participants.

The two subjective rating questions regarding pain and unpleasantness in the pain task will be presented in a truly random order for each trial and each participant.

Sampling Plan

Existing Data

Registration prior to creation of data.

Explanation of existing data

No pre-existing data will be used. A pilot study with nine subjects was conducted before the start of data collection and the upload of this preregistration to test the study procedure, especially for the placebo group. However, this data will not be used in the final analysis.

Data collection procedures

In- and exclusion criteria: The experiment will be conducted with a sample of neurotypical, German-speaking, right-handed young adults, including female and male participants aged between 18 and 35 years (as the same age range was used in previous 'placebo empathy analgesia' studies). Due to ethics regulations of the University of Vienna, we will only recruit people who are currently enrolled in an Austrian university. Each potential participant will be screened for exclusion criteria using a thorough online questionnaire sent via email. Exclusion criteria are a past or present enrollment in academic studies including psychology, pharmaceutics or medicine (veterinary, dental, human, etc.) as well as other medical-related trainings (e.g. nurse), non-normal or non-corrected-to-normal vision, any neurological or psychiatric conditions, past or present substance abuse (alcohol more than daily use, drugs weekly or daily use), the intake of psychopharmacological medication (besides oral contraceptives) within the last three months, past participation in at least one placebo study or a study involving similar deceptive elements, and left-handedness / no handedness preference. The placebo and control group will be matched closely regarding age and trait measures of socio-cognitive and emotional abilities of the following questionnaires (German versions):

- Perspective taking and empathic concern scales of the Interpersonal Reactivity Index (IRI; Davis, 1980)
- Apathy Motivation Index (AMI; Ang et al., 2017)
- Social Value Orientation Scale (SVO; 15 item scale; Murphy et al., 2011)
- Helping Attitudes Scale (HAS; Nickell, 1998; translated into German)
- Short Dark Triad (SD3; Jones & Paulhus, 2014; translated into German)

Participants above the clinical cut-offs of the following questionnaires will be excluded:

- Beck's Depression Inventory II (BDI-II; cut-off = 14; Kühner et al., 2007)
- Autism Quotient (AQ-k; 33 item scale; cut-off = 17; Freitag et al., 2015)
- Toronto Alexithymia Scale (TAS-20; 20 item scale; cut-off = 51; Bach et al., 1996)

Overview of the study procedure: Eligible participants will be sent questionnaires to be completed online prior to coming to the testing session in the lab. They will be asked to abstain from alcohol, drugs, and any medication intake (except oral contraceptives) 24 hours before the experiment and to abstain from smoking, food, caffeine, and any drinks other than water 1 hour before the experiment. Participants will then take part in one behavioral session in groups of two (the other participant being a confederate posing as the second participant and when being named, of the same sex as the real participant). In the testing session, the first part will be dedicated to introduction, instructions, informed consent, role assignment and calibration of individual pain threshold and maximum effort (see below for a thorough description). Depending on the group, this will be followed by the placebo induction (placebo group) or an equal waiting time (control group), where magazines are available to read. After a second effort calibration and the placebo conditioning procedure (or a second equal waiting time for the control group), participants will complete all tasks on a computer, with the participant and the confederate sitting in separate rooms. The task order will be fixed, starting with a training of the pain task, where only the confederate receives stimulation (total of 4

shocks, 2 painful and 2 non-painful) and the participant rates this stimulation regarding pain intensity and own unpleasantness (see below), followed by the completion of the prosocial effort task and the pain task on a computer. After this, participants will complete a third task unrelated to this project (see preregistration of the project 'The Effects of Placebo Analgesia on Interoceptive Abilities' by Helena Hartmann for a description of this task). The session will end with follow-up questions and feedback from the participant. Anonymity of the participants (except for the sex and name) is ensured over the whole course of the experiment to limit the effects of reputation and reciprocity in relation to the confederate for the prosocial effort task. Participants will therefore be told that they arrived a few minutes apart from each other, see only each other's gloved hands during the role assignment and leave separately at different time points. The whole experiment will last approximately 3 hours. Participants will be compensated with 35 Euros for their participation. The local ethics committee of the University of Vienna approved all procedures beforehand.

Role assignment: First, the participant and the confederate will be asked to complete a "random role assignment procedure" that chooses who will be the "Receiver" and who the "Giver" of pain in the prosocial effort task (similar to Crockett et al., 2015; Lockwood, Hamonet, et al., 2017). The participant and the confederate each draw a ball from a box that reveals their role. Participants are positioned on either side of a door and wear gloves during the procedure so they cannot see each other's hands and arms or know each other's identities (e.g., age, race, etc.). They are instructed not to speak and direct their gaze away from the box to draw their roles silently at the same time. Since this study investigates prosocial behavior, the real participant will always be assigned the role of "Giver" and the confederate always the role of "Receiver", independent of the color of the ball they draw.

Pain calibration: The pain calibration will use a procedure similar to the one used in Rütgen, Seidel, Riečanský, et al. (2015) and Rütgen, Seidel, Silani, et al. (2015) where

electrical stimulation is given to the dorsum of the non-dominant, left hand in multiple trials, moving up stepwise a rating of 0 = 'not perceivable' until the stimulus is rated as 8 = 'extremely painful but bearable' (beginning at a low intensity of 0.05 mA, step size individually chosen for each participant, so that each rating is experienced at least once). This will be repeated a second time with small breaks in between to avoid habituation/sensitization and is followed by varying (seemingly "random") stimulation in the before calibrated rating range from 1 – 8 to gain a valid average for values the participant rated as 1 = 'noticeable but not painful', 4 = 'medium painful' and 7 = 'very painful'. The average intensities rated as 1 and 7 will then be used in the pain task for non-painful and painful stimulation, respectively. The average intensities rated as 1 and 4 will be used during the conditioning procedure (see below).

Effort calibration: Effort will be calibrated using the maximum voluntary contraction (MVC) task, where participants are asked to grip a handheld dynamometer with their dominant, right hand with as much force as possible two times in a row for three seconds with small breaks in between, while seeing live feedback of their exerted effort on the screen. This will ensure that the effort levels used in the task will be relative to participants' individual strength. Participants will be thoroughly instructed to always hold the device in a certain way (lower arm and hand on a cushion on the table, dorsum of the hand directed towards the table) and to maintain this position during the task to keep the MVC level constant (as the MVC can be affected by different holding positions of the dynamometer). During the calibration procedure, the participants will be watched by an experimenter to check for correct execution and corrected if needed, e.g., to press stronger next time or hold the device differently. Participants will be urged to press as strongly as they can by telling them that the stronger they press, the more money they will gain (in reality, all participants receive 35 Euros). After this, participants will train twice to press until and over a certain

effort level (indicated by a yellow line) and then experience each effort level used later in the task (30, 40, 50, 60 and 70 % of their MVC). Regarding the latter, they will be asked to complete two items from the NASA Task Load Index (Hart & Staveland, 1988); Physical Demand: "How physically demanding was the task?", Effort: "How hard did you have to work to accomplish your level of performance?") and one additional question (Unpleasantness: "How unpleasant was it for you?") for each of the 5 effort levels and the baseline level (i.e. not exerting any effort but holding the dynamometer in the hand). After the placebo induction, this whole calibration procedure will be repeated to compare pre- and post-placebo MVC and NASA Task Load Index ratings. For the prosocial effort task, the maximum of the four MVC trials (two before and two after the placebo induction) will be used as the individual MVC informing the five effort levels. At the end of the prosocial effort task, the MVC will be measured again once, but this time as an operationalization of the participant's personal effort motivation to win money for him-/herself. At the end of the session, we will repeat the whole effort calibration a third time to measure changes in effort motivation / fatigue over time.

Placebo induction: The placebo group will receive the placebo induction using a pill presented as an "effective and powerful painkiller" and further verbal suggestions by a medical cover (presented as a doctor working at the faculty of psychology) and, after a waiting time of 10 minutes for the pill "to take effect", a conditioning procedure in regard to the treatment. This conditioning procedure will involve the participants receiving electrical stimulation on the same hand using the same electrode location as in the calibration. Participants will be told they will receive high stimulation intensities they rated as very painful before, but in reality, they will receive stimulation with a medium intensity (rated as 4 before) and corresponding feedback (e.g., "This was rated as more painful/very painful before") to suggest and induce pain reduction. These conditioning trials will be repeated for a

minimum of two and up to a maximum of four times until the subject doesn't respond with values higher than 5 to the conditioning stimulus, i.e., he/she believes a pain reduction has taken place. The control group will not receive a pill or any type of induction procedure but will have an equal waiting time to keep the whole session length as homogeneous as possible between the two groups. In reality, the pill will contain no active analgesic/pain-reducing components, but a natural sugar-alcohol (Mannitolum, 40G per pill).

Prosocial effort task: The prosocial effort task is adapted from the one used by Lockwood, Hamonet, et al. (2017): Each trial, participants have to make a choice between a no effort (0 % of MVC), no helping (baseline) offer where the confederate will receive a fixed amount of 6 shocks, and a higher effort, helping (variable) offer, where they must exert effort (either 30, 40, 50, 60 or 70 % of their individually calibrated MVC) to help the confederate by avoiding punishment (reduce the number of shocks the confederate receives by either 1, 2, 3, 4 or 5). If participants chose the variable offer, they have a 3-second time window to directly exert effort using the dynamometer and reach the required effort level for at least 1 second during this time window. Visual real-time feedback is provided during this period to show participants how much effort they are exerting in comparison to the effort they have to reach (indicated by a yellow line). After exerting the chosen effort, participants receive feedback of how much they helped the confederate (i.e., that the confederate allegedly directly receives the chosen stimulation which is shown by displaying one appearing red lightning for each given shock to make it more realistic that actual shocks are given to the confederate). If the participant chooses to exert effort, but fails to reach the chosen effort level, or if the participant doesn't make a choice, this trial will be deemed a "fail trial" and the confederate allegedly receives 10 shocks (it will be communicated clearly to the participants that this should be avoided, and it is always better to (1) make a decision and (2) reach the chosen effort). The minimum of shocks the confederate will allegedly receive is 1 and the maximum

10, but the participant as the "Giver" never receives any pain in this task. Importantly, all trials will be the same length independent of the choices the participant makes. Participants will complete three blocks of 25 trials each, with breaks of 90 s in between. All participants will exert the effort with their right hand and make the choices with two fingers of their left hand placed on a keyboard. In the breaks, the participants are instructed to sit still and relax their hand as well as to not hold the dynamometer. At the end of the prosocial effort task, participants will have the opportunity to press as hard as they can to win bonus money for themselves that will be added to their compensation (total compensation will always be 35 Euros). This will be used as a control measurement of self-related effort motivation between the groups.

Pain task: The pain task is a shortened version of the one used in Rütgen, Seidel, Silani, et al. (2015) with a total of 20 trials (5 per condition). Participants will rate painful and non-painful electrical stimulation that they either receive themselves or that the confederate allegedly receives (for ratings see "Measured variables" below). The task will look the same as in previous studies, with two exceptions: (1) not showing pictures of the confederate in pain to keep participants anonymity and (2) using "SHE" or "HE" and "YOU" in big letters instead of arrows as cues. This will later act as a manipulation check for evaluating analgesic effects on first-hand pain. However, since this task is completed relatively late in the experiment compared to the placebo induction, placebo effects could be reduced compared to the beginning of the experiment. To counteract this, we will assess analgesic effects on empathy for pain at two time points, before and after the prosocial effort task and will use a thorough procedure for identifying non-responders to the manipulation (see below under stopping rule).

Recruitment: We will recruit subjects by means of advertisements around the different universities in Vienna, popular student locations, on different websites online (Forums,

Facebook groups, etc.) and via an existing database of interested study participants implemented in our department (https://labs-univie.sona-systems.com).

Sample size

Our total target sample size is 90 participants (45 participants with a balanced sex ratio per group), excluding non-responders to the placebo manipulation (see below under stopping rule). Additionally, we tested 9 pilot subjects with the complete setup prior to starting the study.

Sample size rationale

For this study, precise power calculations were not possible due to the absence of previous studies investigating our research question and thus a lack of fitting effect size estimates. We therefore based our group sizes on previous studies using similar versions of the effort task (Crockett et al., 2015; Lockwood, Hamonet, et al., 2017).

Stopping rule

Potential dropouts, including placebo analgesia non-responders in the placebo group (estimated at maximum 16 - 25 % based on previous studies: Rütgen, Seidel, Riečanský, et al., 2015; Rütgen, Seidel, Silani, et al., 2015), will be replaced. Data collection will be terminated when a sample size of 45 participants in each group is reached.

Non-responders will be determined by procedures equal to the ones used in Rütgen, Seidel, Silani, et al. (2015). In short, a combination of three measures will be employed: First, we will record any verbally expressed doubts about the analgesic effects of the pill or pain medication in general as well as about the study setup (e.g., confederate or other deceptive parts) after the experiment by means of feedback questions. If a participant expresses doubts in any of these domains, we will ask him or her to elaborate these doubts further and participants with strong doubts relevant to the manipulation will be excluded. Second, differences of the belief scores about the effectiveness of the placebo before and after the

induction procedure as well as at the end of the session will be analyzed (using the same criteria as in the previous studies). Exceptionally low total belief scores (sum of pre and post conditioning scores lower than 66.6, sum values can range from 0 to 200) and strong decreases between first and second measure (pre score minus post score bigger than 33.3) will serve as a measure for lack of responding. Third, we will take the number of placebo conditioning trials into account. All participants will complete a minimum of two trials. If participants respond with a value greater than 5 on a 9-point rating scale from 0 = 'not noticeable' to 8 = 'extremely painful, but bearable' to the conditioning stimulus (delivered at a medium intensity of 4), we will deem the conditioning trial as non-successful, wait another few minutes for the medication to take effect, and then try again. This will be repeated for a maximum of four times until participants respond with values of 1-5 to the conditioning stimulus. If more than three of these trials are necessary, this will be taken as an indication of non-responding to the placebo treatment.

Variables

Manipulated variables

General: Treatment (2 between-subject levels: placebo group, control group). Pain task: Intensity (2 within-subject levels: pain, no pain), Target (2 within-subject levels: self, other). Prosocial effort task: Effort (5 within-subject levels: 30, 40, 50, 60 or 70 % of MVC), Helping (5 within-subject levels: reducing number of shocks by 1, 2, 3, 4 or 5)

Measured variables

The ratings in the pain task will target two different aspects of empathy: (1) Rating of the own subjective degree of unpleasantness when seeing another person in pain ('other unpleasantness'), tapping into affective sharing and vicarious distress; and (2) rating of the intensity of the pain felt by the other ('other pain') as a more cognitive-evaluative aspect of empathy. These two variables will be measured via self-report by asking the participants after

the electrical stimulation of the other person: 'How unpleasant did it feel for you when the other person was stimulated?' (on a 9-point rating scale from 0 = 'not at all' to 8 = 'extremely unpleasant') as well as 'How painful was this stimulation for the other person?' (on a 9-point rating scale from 0 = 'not noticeable' to 8 = 'extremely painful'). For first-hand stimulation, we will ask: 'How painful was this stimulation for you?' (on a 9-point rating scale from 0 = 'not noticeable' to 8 = 'extremely painful').

For each trial of the prosocial effort task, we will measure the following dependent variables (as per Lockwood, Hamonet, et al. (2017): Proportion of 'variable offers' chosen as the willingness to put in other-related effort, and real force exerted as a measure of how energized people's actions are. Additionally, we will measure reaction time during the choice period as a third measure of motivation.

We will measure and explore differences in physiological data between the groups and conditions in the form of skin conductance and heart rate during all trainings and tasks using Mobi, a compact measurement system for electrophysiological signals (Twente Medical Systems International, Netherlands).

To control for concerns of reputation and reciprocity, we will gather information after the session on subjects' beliefs whether their identity will not be revealed to the receiver, whether their decisions would be kept confidential and whether their decisions were "observed" during the experiment.

We will also ask again about beliefs regarding the effectiveness of the medication and doubts regarding the study setup.

In general, the German versions of the following questionnaires will be administered either at least one week prior to the testing session (marked with *) or during the testing session (marked with **):

- Vicarious Pain Questionnaire (VPQ; Grice-Jackson et al., 2017a)*

- Questionnaire of Cognitive and Affective Empathy (QCAE; Reniers et al., 2011)*
- Interpersonal Reactivity Index (IRI; Davis, 1980)*
- Social Value Orientation Scale (SVO; 15 item scale; Murphy et al., 2011)*
- Apathy Motivation Index (AMI; Ang et al., 2017)*
- Helping Attitudes Scale (HAS; Nickell, 1998; translated into German)*
- Toronto Alexithymia Scale (TAS-20; 20 item scale; Bach et al., 1996)*
- Autism Quotient (AQ-k; 33 item scale; Freitag et al., 2015)*
- Beck's Depression Inventory II (BDI-II; Kühner et al., 2007)*
- Short Dark Triad (SD3; Jones & Paulhus, 2014; translated into German)*
- Spielberger State-Trait-Anxiety Inventory (STAI; 20 item scale in the trait version; Spielberger et al., 1999)*
- Lifetime Depression Assessment Self-report (LIDAS; Bot et al., 2017)*
- Positive and Negative Affect Schedule (PANAS; Krohne et al., 1996; assessed 3 times over the course of the testing session)**
- Multidimensional Assessment of Interoceptive Awareness (MAIA; Mehling et al., 2012)**

Indices

All trial ratings of one condition will be combined into separate means. Participants number of alternative choices will be converted into a 'proportion of variable offers chosen'.

Analysis Plan

Statistical models

Regarding the behavioral data, we will use a GLM-based approach. In a first step, we want to replicate the analyses of previous similar studies (Lockwood, Hamonet, et al., 2017; Rütgen, Seidel, Silani, et al., 2015) using analyses of variance (ANOVAs). In a second step,

we want to explore possibly more sensitive methods like linear mixed models (LMMs) and computational modelling to analyze the results.

Pain task: In the first analysis, the dependent variable is represented by the self- and other-directed pain ratings. A second analysis will include the self-directed pain ratings as well as the other-directed unpleasantness ratings as the dependent variable. The independent variables will be treatment, target, and intensity in both analyses. The focus in these two analyses will be on significant treatment*intensity interactions (= indication that placebo analgesia changes the difference between pain and no pain conditions) and non-significant 3-way interactions between treatment*intensity*target (= no difference in the placebo effect between first-hand and empathy for pain).

Prosocial Effort task: In the main analysis, the proportion of variable offers chosen ("option chosen") will be used as a dependent variable, while analyses of raw force data and reaction times will be carried out separately. The independent variables will always be effort and helping. Regarding "option chosen", we expect to find main effects of effort as well as helping. In other words, participants will choose the alternative option less with increasing effort and will choose the alternative option more with increasing helping in both treatments. More specifically, we will check whether the placebo and control group differ significantly for all outcome variables:

If (2a) placebo analgesia reduces prosocial behavior, we would predict a main effect of treatment where the placebo group is less likely to choose the variable (higher effort, higher helping) option than the control group.

If (2b) placebo analgesia increases prosocial behavior, we would predict a main effect of treatment where the placebo group is more likely to choose the variable (higher effort, higher helping) option than the control group.

We don't have any specific directional hypotheses regarding interactions of treatment with effort or helping, so these will be exploratory. It could e.g., be, that the effect regarding prosociality in the placebo group (whatever direction) is more pronounced at lower or higher effort levels (treatment x effort interaction) and/or more pronounced at lower or higher helping levels (treatment x helping interaction) or dependent on both (treatment x effort x helping interaction).

We will also compare the two groups regarding the effort they put in for themselves to gain extra money at the end of the prosocial effort task (measured as one MVC-trial). If placebo analgesia acts exclusively on other-related effort motivation, i.e., prosocial behavior, we expect no group differences in self-related effort. If, on the other hand, the placebo reduces effort motivation in general, we expect lower values for the placebo group in this measure.

For the LMMs, the fixed effects structure will generally be constituted by the above mentioned between-subject factor treatment and the within-subject factors for each task. Subject (id) will be used as a random factor. We will start with the maximal random effects structure and explore this one (Barr et al., 2013) as well as more parsimonious models ("optimal random effects structure") using model selection (Matuschek et al., 2017). For the pain task, the general analysis approach will look as follows (DV will be the pain ratings): DV ~ treatment * target * intensity + (target * intensity | id). For the prosocial effort task, the general analysis approach will look as follows (DV will be either "option chosen" as a binary variable, raw force, or reaction time): DV ~ treatment * effort * helping + (effort * helping | id).

As in Lockwood, Hamonet et al. (2017), computational modeling will also be used to quantify how much participants devaluate prosocial behavior (operationalized here as pain avoidance for another person, in accordance to "reward" in Lockwood, Hamonet, et al.

(2017) depending on the amount of effort they need to exert. Following a proposed categorization by Crüwell, Stefan, et al. (2019), we will employ model application (i.e. defining different models using combinations of parameters) and model comparison (i.e. comparing them to each other). Models will be fitted to the data using Markov-Chain-Monte-Carlo (MCMC) sampling with a 'softmax' linking function. Parameters in the model will include the discount parameter, K, which characterizes the degree to which the pain avoidance/prosocial behavior is devaluated by effort, and a noise parameter (inverse softmax temperature), β, which characterizes the stochasticity of choices. Higher K values indicate higher discounting in valuation of pain avoidance (i.e., less effort exertion/less prosociality). Higher β values indicate higher consistency in choice behavior . Models which analyze the discount and noise parameters from the placebo group and the control group separately (i.e., K_Placebo, K_Control, β_Placebo, β_Control) will be compared to models which do not make this distinction. The possible combinations of K and β are (1) a model with one discount (K) and one softmax (β) parameter for placebo/control, (2) a model with one discount (K) and separate softmax (β's) parameters for placebo and control, (3) a model with separate discount (K's) parameters for placebo and control and one softmax (β) and (4) a model with separate discount (K's) parameters and separate softmax (β's) parameters for placebo and control. The modeling part of this study will be oriented on previous studies in this domain: First, we want to mimic the analyses outlined in Lockwood, Hamonet, et al. (2017) using individual fit. Second, we would like to explore the data using hierarchical fit.

Transformations

None.

Inference criteria

We will use an alpha level of 0.05, two-tailed, and a 95 % confidence interval for determining if the statistical tests suggest that the results are significantly different from those

expected if the null hypothesis were correct. Significant interactions, if not sufficiently explained by the analysis plan and in particular by the planned comparisons, will be followed-up (and corrected for multiple comparisons).

Data exclusion

In general, we will use winsorizing to handle outliers. Participants with choices reflecting disengagement from the task, like choosing the baseline option in 100 % of all trials (i.e., never exerting effort) or failing to exert effort due to fatigue after some time, will be excluded. Additional exclusion criteria are expressed doubts about the setup of the study, and for the placebo group also low belief scores regarding the effectiveness of the placebo treatment and strong decreases between the first and second effectiveness measure, as well as more than three needed conditioning trials (see above for a thorough description of placebo non-responder identification).

Missing data

Subjects with missing or incomplete data (i.e., more than 10 % "failed" trials in the prosocial effort task) will be excluded from the analysis.

Exploratory analysis

We expect that certain demographic or personality traits may be related to our dependent variables. Therefore, we will look for relationships between sociodemographic and trait variables (sex, empathy, vicarious pain, first-hand pain processing, apathy, social value orientation, mood, prosociality, anxiety, depression, psychopathy, autistic traits, alexithymia), and the primary outcome measures of empathy and prosocial behavior (choice, effort exerted, reaction time, other pain/unpleasantness ratings).

For example, individuals differ in how much they value other people's rewards relative to their own (prosocial/altruistic vs. individualistic orientation). We will measure this orientation using the Social Value Orientation (SVO) Scale (R. O. Murphy et al., 2011).

Regarding our study setup, people who have a more altruistic SVO might show a different effect regarding prosocial behavior when under the influence of a placebo than someone with a more individualistic SVO. To this end, we want to run the above-mentioned analyses controlling for SVO.

Similarly, we want to control for individual levels of behavioral/self and social/other motivation measured with the Apathy Motivation Index (Ang et al., 2017), as it was shown to be associated to exerting effort, empathy and willingness to engage in social behavior. It could therefore be that any results are driven by individual levels of self/other motivation rather than the placebo itself.

After the scanning session, we will also assess previous experiences and associations with pain medication. We will also check whether the ratings regarding the effectiveness of the placebo treatment pre- and post-conditioning changed significantly.

Furthermore, we will investigate experimenter-effects (Rosenthal, 1976) by asking about expectations regarding the results (whether the participants had any expectations or what expectations he/she thinks the experimenters of the study had).

Since fatigue plays an important role in effort tasks (Müller & Apps, 2018), we want to investigate fatigue effects between groups and over the course of the experiment. We will therefore analyze differences in the three effort calibrations and mood changes over the course of the session within and between the two groups. In this context, we will also investigate changes in physical strength (measured as MVC) due to the placebo manipulation.

Summary

Provide a narrative summary of what is contained in this registration or how it differs from prior registrations. If this project contains documents for a preregistration, please note that here.

This is an addendum to the preregistration of this project (https://osf.io/g3acp), uploaded on August 25th, 2019. There, we wrote: "In the first analysis, the dependent variable is represented by the self- and other-directed pain ratings. A second analysis will include the self-directed pain ratings as well as the other-directed unpleasantness ratings as the dependent variable. The independent variables will be treatment, target, and intensity in both analyses. The focus in these two analyses will be on significant treatment*intensity interactions (= indication that placebo analgesia changes the difference between pain and no pain conditions) and non-significant 3-way interactions between treatment*intensity*target (= no difference in the placebo effect between first-hand and empathy for pain)."

This was a mistake on our part since the use of the factor target (self vs. other) only applies to the first analysis where self- and other-related pain ratings are compared. Regarding unpleasantness, we did not collect other-, but only self-related unpleasantness ratings. Since pain and unpleasantness aim to measure two different aspects of the empathic response, it does not make sense to compare them within one analysis. The correct analysis is therefore an ANOVA using the unpleasantness ratings as the DV and the factors intensity and treatment (see also our previous preregistration where we preregistered the correct analysis: https://osf.io/uwzb5).

Furthermore, we would like to add additional information regarding the stopping rule. We wrote in the original preregistration that we will exclude non-responders to the placebo induction based on three criteria, the first being "any verbally expressed doubts about the analgesic effects of the pill or pain medication in general as well as about the study setup (e.g., confederate or other deceptive parts) after the experiment by means of feedback questions". Under "Data exclusion", we wrote "Additional exclusion criteria are expressed doubts about the setup of the study, and for the placebo group also low belief scores regarding the effectiveness of the placebo treatment and strong decreases between the first

and second effectiveness measure, as well as more than three needed conditioning trials (see above for a thorough description of placebo non-responder identification)."

Since our original preregistration might seem unclear regarding this, we want to clarify that the exclusion criteria "doubts" applies both to participants in the placebo and the control group. In addition to the already preregistered non-responder criteria for the placebo group, we will exclude and replace any participant expressing serious doubts about any deceptive element of the study (e.g., not believing that the second person existed or received shocks). This will make sure that the final sample of 90 participants only consists of participants who believed the cover story.

The data collection of this project is currently ongoing, and we have not started analyzing at the data yet. We recently noticed these mistakes/omissions and wanted to disclose them as soon as possible by adding them to the preregistered plan before beginning with data inspection and analysis.

4.2 Study 3: Placebo analgesia reduces costly prosocial helping to lower another's pain

Helena Hartmann[ab], Paul Forbes[a], Markus Rütgen[a], & Claus Lamm[a*]

[a] *Social, Cognitive and Affective Neuroscience Unit, Department of Cognition, Emotion, and Methods in Psychology, Faculty of Psychology, University of Vienna, Vienna, Austria*

[b] *Social Brain Laboratory, Netherlands Institute for Neuroscience, Royal Netherlands Academy of Arts and Sciences, Amsterdam, The Netherlands*

* *Corresponding author*

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4.2.1 Abstract

Administration of painkillers has been shown to lower pain empathy, but whether this also reduces prosocial behavior is not known. In this preregistered study, we investigated whether inducing analgesia through a placebo painkiller reduced effortful helping. When given the opportunity to reduce the pain of another person, individuals experiencing placebo analgesia made fewer prosocial choices, helped less quickly, and exerted less physical effort when helping, compared to control participants with unaltered pain sensitivity. Furthermore, self-reported empathic unpleasantness positively correlated with prosocial choices across the whole sample. Reduced pain sensitivity thus not only influences empathy, as previously shown, but also negatively impacts prosocial behavior. Given the importance of prosociality for social cohesion, these findings have broad potential implications for both individuals under the influence of painkillers and for society at large.

4.2.2 Statement of Relevance

The widespread use and abuse of opioids has been recognized as a major individual and public health threat. One under-investigated aspect of this crisis is how the use of painkillers affects our social interactions. Previous studies have highlighted detrimental effects of

psychopharmacological interventions targeting the opioidergic system on empathic abilities. However, it is unclear whether reduced pain sensitivity also leads to changes in prosocial behavior. In this experimental behavioral study, we tested whether lowering pain sensitivity by means of placebo analgesia lowers helping behavior, measured by exerting physical effort to reduce another's pain. Placebo analgesia not only decreased the willingness to invest effort, but also slowed reaction times and decreased the actual effort exerted when helping. These detrimental effects of analgesia on prosociality may have far-reaching implications, for individuals under the influence of painkillers, but also for social cohesion in societies with over-consumption of analgesics.

4.2.3 Introduction

The frequent (ab)use of opioid painkillers has been recognized as a global health concern, with negative effects on individuals as well as society (Vadivelu et al., 2018 for a review). Pain medication has widespread effects on our own pain perception, but also impacts how we emotionally resonate with conspecifics (Nummenmaa & Tuominen, 2017 for a review). Past research has causally linked an upregulation of the opioidergic system to reduced pain empathy, suggesting that the intake of painkillers may have detrimental effects on social motivation and subsequent behaviors (Rütgen, Seidel, Silani, et al., 2015; Vecchio & De Pascalis, 2021). While the effects of psychopharmacological manipulations on first-hand and empathy for pain have been consistently demonstrated, their potential downstream effects on prosocial behavior remain to be established. Understanding these effects is fundamentally important, as these processes are not only key drivers of group bonding and social cohesion, but also strongly contribute to individual and societal wellbeing (de Waal, 2008 for a review; Rameson et al., 2012).

A series of experimental studies has shown that individuals whose first-hand pain sensitivity was reduced by placebo analgesia (i.e., inducing beliefs that an inert pill acts as a

potent painkiller) showed reductions in self-reported pain empathy and decreased activation in key areas of the brain's 'pain empathy network' (Rütgen, Seidel, Riečanský, et al., 2015; Rütgen, Seidel, Silani, et al., 2015; Rütgen et al., 2021; Vecchio & De Pascalis, 2021). Of note here is that placebo mechanisms in first-hand pain (Petrovic et al., 2002; Zubieta et al., 2005; Zubieta & Stohler, 2009) and pain empathy (Rütgen, Seidel, Silani, et al., 2015; Rütgen et al., 2018, 2021) have consistently been linked to an upregulation of the endogenous opioid system. Single-dose administration of acetaminophen, a non-opioidergic painkiller (i.e., Paracetamol, Tylenol), also reduced self-reported empathy (Mischkowski et al., 2016, 2019). Thus, psychopharmacological manipulations of our own pain state causally influence how we share others' pain states.

Empathy and prosociality are closely linked, with higher trait and state empathy acting as powerful drivers of prosocial tendencies and actual helping behaviors (Brethel-Haurwitz et al., 2018; Crockett et al., 2015; Lockwood et al., 2014; Lockwood, Ang, et al., 2017; Morelli et al., 2014; Story et al., 2020; see de Waal & Preston, 2017; Eisenberg et al., 2011; Eisenberg & Miller, 1987; Lamm et al., 2019 for reviews). A connection between pain empathy and subsequent helping behavior was recently shown by Gallo et al. (2018) who found that disrupting primary somatosensory cortex altered the coupling between pain perceived in another person and monetary donations to reduce that pain. However, whether altering first-hand pain sensitivity through analgesia also impacts helping has not been systematically investigated. Answering this question will have major implications, as it could demonstrate that painkillers not only interfere with how we represent and understand others' emotions, but that they also affect how we behave towards people around us. The objective of this study was, thus, to investigate how reducing pain sensitivity through a well-established placebo analgesia manipulation influences costly helping. We preregistered that placebo analgesia would modulate prosocial behavior (see Hypotheses in the preregistration). This

would be evidenced by a reduced willingness to choose an effortful option to reduce another's pain, longer reaction times when making such choices, and a reduced amount of actual force exerted. However, we also considered the possibility that placebo analgesia could increase prosocial behavior in the preregistration.

A major challenge in measuring prosocial behavior is that many existing paradigms involve one-shot tasks, such as picking up dropped pens or donating part of a monetary endowment (Thielmann et al., 2020, 2021 for overviews). These tasks may not capture moment-by-moment decisions necessary in everyday life. Moreover, they largely rely on self-report, which are prone to social desirability effects and often measure hypothetical intentions rather than actual behavior (Martí-Vilar et al., 2019; Pfattheicher et al., 2022 for reviews). To overcome these limitations, recently developed experimental paradigms require participants to invest physical effort over multiple trials (Cameron et al., 2022; Contreras-Huerta et al., 2020 for reviews). These tasks show that individuals vary their helping based on how much effort they need to put in, and how rewarding that helping is (termed "prosocial apathy" in Lockwood, Hamonet, et al., 2017, 2021). Furthermore, participants' decision-making in the form of choice behavior has been increasingly used in addition to subjective indicators such as ratings to more comprehensively measure the full extent of prosocial behavior (Crockett et al., 2015; Lockwood et al., 2016; Story et al., 2020). We therefore developed a paradigm to test whether placebo analgesia affects the effort individuals exert to reduce another's pain.

4.2.4 Materials and Methods

Open Practices Statement

As suggested by Simmons et al. (2012), we report how we determined our sample size, all data exclusions, all manipulations, and all measures in the study. This study was preregistered on the Open Science Framework (OSF) prior to data collection (Hartmann & Lamm, 2019;

preregistration and addendum, deviations listed in the Supplement). All data and code to analyze the data and reproduce the figures are available on the OSF.

Procedure

Session overview. Participants took part in one behavioral session in pairs, with the other participant being a gender-matched confederate posing as the second participant (Figure 17 for an overview and Supplement for more detailed procedure). All participants received the same financial compensation, and the ethics committee of the University of Vienna approved all procedures (application number 00412).

Role assignment and calibrations. The participant and confederate were asked to complete an "random role assignment procedure" determining the roles of 'Receiver' and 'Decider' in the prosocial effort task, as per previous studies (Crockett et al., 2015; Lockwood, Hamonet, et al., 2017). While the participant who was always chosen as the Decider would make choices involving the other person receiving pain, the confederate as the Receiver would receive electrical stimulation. All subsequent steps relate to the real participant as the Decider. Anonymity (except for gender and name) was ensured over the whole session to limit the effects of reputation and reciprocity (as per Lockwood, Hamonet, et al., 2017, participants might act more prosocial just because they think they might to meet the other person later again). Then, we employed a pain calibration as in Rütgen, Seidel, Silani, et al. (2015) where electrical stimulation was given to the dorsum of the non-dominant, left hand to gain average stimulation intensities between 0 (not perceivable) and 8 (extremely painful) using a Digitimer DS5 Isolated Bipolar Constant Current Stimulator (Digitimer Ltd, Clinical & Biomedical Research Instruments). After this, effort was calibrated using maximum voluntary contraction (MVC), whereby participants were asked to grip a handheld dynamometer (Vernier, Beaverton, OR, USA) in their dominant, right hand with as much force as possible. This ensured the effort levels used in the task were relative to each

participants' individual strength. The effort calibration was completed three times (before and after the placebo induction and at the end of the session). To measure changes in motivation and fatigue over time, we also measured each participant's MVC twice in a row at the same three time points as the NASA ratings.

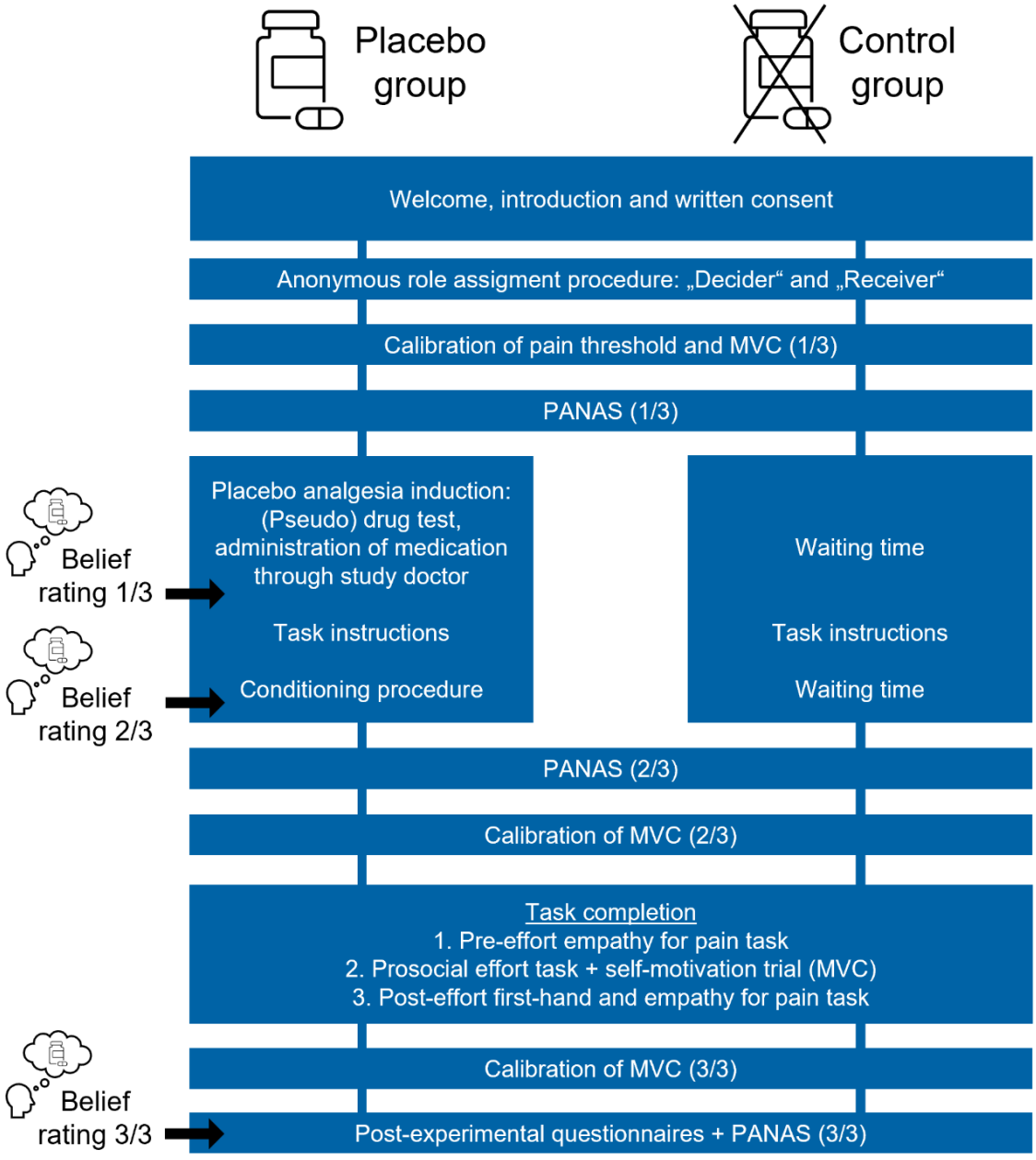

Figure 17. Overview of the experimental session for each group. Real participants were always chosen as the "Decider". Participants in both groups underwent the same steps, except for the placebo analgesia induction. During this time, the control group had an equally long waiting time. Belief ratings about the effectiveness of the pill were only collected from the placebo group. PANAS = Positive and Negative Affect Schedule (Krohne et al., 1996); MVC = maximum voluntary contraction. Figure taken from Hartmann et al. (2022).

Placebo analgesia induction. Next, the placebo group underwent a placebo analgesia induction using an inert pill presented as an "effective and powerful painkiller" and similar verbal suggestions by a medical student acting as the study's medical doctor. After a waiting time of 10 minutes for the pill "to take effect", classical conditioning was performed to amplify the placebo effect. Participants received stimulation with a medium intensity (rated as 4 in the pain calibration), coupled with corresponding feedback suggesting substantial pain reduction by the pill (e.g., "This stimulus was rated as very/extremely painful before"). To measure placebo responding over the course of the session, we collected three belief ratings about the effectiveness of the "medication". The control group did not undergo any such manipulations but had equally long waiting times to keep the overall session length the same. We additionally collected positive and negative mood ratings from both groups at three times using the Positive and Negative Affect Schedule (PANAS; Krohne et al., 1996).

Prosocial effort task. The prosocial effort task was adapted from Lockwood, Hamonet et al. (2017) and Crockett et al. (2015): Each trial, participants were asked to make a choice between a baseline "rest" offer (no effort necessary) where the confederate received a fixed amount of six shocks, and a "work" offer involving exertion of physical effort (30, 40, 50, 60 or 70 % of their MVC) to help the other participant (reducing the number of shocks the confederate would receive by either 1, 2, 3, 4 or 5 shocks; Figure 18). Every work offer combination (5 effort levels x 5 shock reduction levels = 25 levels) was presented three times, leading to 75 choices. If the participants chose to help, but failed to reach the chosen effort level, or when they did not respond within 3 seconds, the confederate received 10 shocks (see Supplement for more information on these 'fail trials', which did not differ between groups, all p's > .055). In fact, the 'Receiver' never received pain in this task. This deception was used to create a believable and realistic social situation where decisions of the participants would ostensibly have real and live consequences for another person, to induce a

conflict between costly investing of effort and helping to reduce another's pain. At the end of the prosocial effort task, MVC was measured again, but this time it was incentivized to determine participant's personal effort motivation to earn a financial bonus for themselves. This was used as a control measurement to assess whether the placebo influenced self-related motivation. As per our preregistration, if placebo analgesia acted exclusively on prosocial motivation, we would expect no group differences on this task. If, on the other hand, placebo analgesia modulates motivation to exert effort in general, we would expect a group difference.

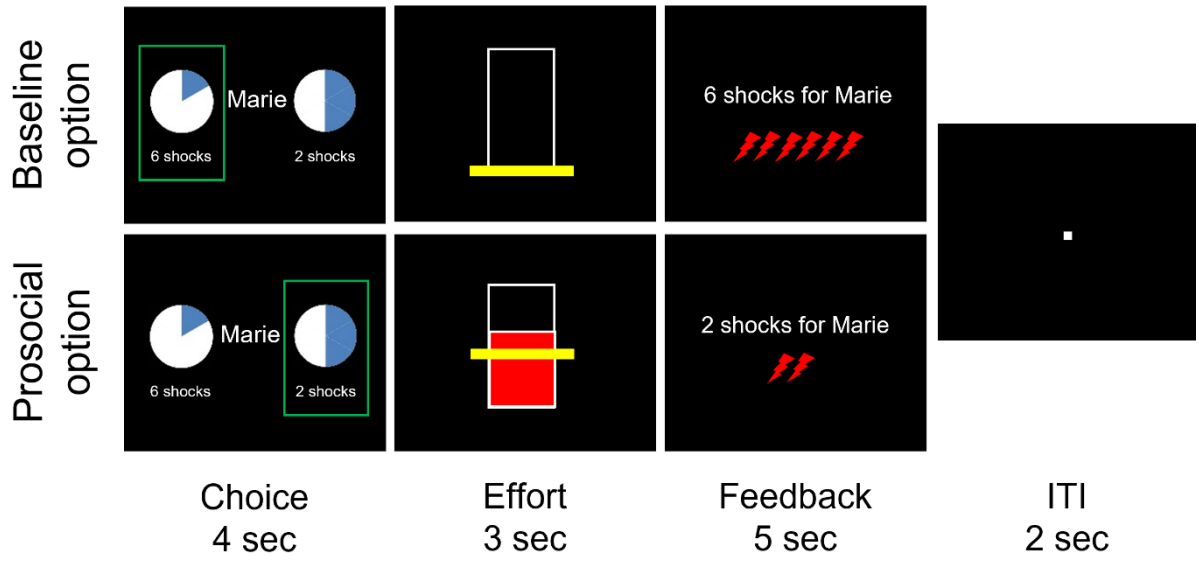

Figure 18. In the prosocial effort task, the real participant as the "Decider" had to make a choice between a baseline rest option (no effort exertion) and a more effortful prosocial option: In the latter case, participants were asked to exert either 30, 40, 50, 60 or 70% of their maximum voluntary contraction (MVC; the more filled the circle the greater the effort level and 1/6th filled as the baseline option and each additional slice representing a higher effort level) to reduce the number of shocks the other participant was going to receive in that trial by 1, 2, 3, 4 or 5 (indicated below the circle). This led to 5 x 5 = 25 possible combinations, each of which was presented three times. After the choice, participants immediately exerted their chosen effort while receiving visual real-time feedback to show how much effort they were exerting in comparison to the effort they had to reach (indicated by a yellow line, which had to be reached for at least 1 out of 3 sec). After the 3 seconds had elapsed, they received feedback on the shocks the other participant (allegedly) got. The feedback included text and red lightning-shapes, which appeared one after the other to reinforce the belief that shocks were given to the Receiver in real time. All information given on-screen in the task was in German. Figure taken from Hartmann et al. (2022).

First-hand and empathy for pain task. To evaluate analgesic effects on first-hand and empathy for pain, participants rated painful and non-painful electrical stimulation (rated as 1 = 'noticeable but not painful' or 7 = 'very painful' in the pain calibration) that they either

received themselves (self trials) or that the confederate received (other trials; Figure 19; Rütgen, Seidel, Riečanský, et al., 2015). Participants completed a short pre-effort empathy for pain task (two pain and two no-pain trials) before the prosocial effort task (as per the "Other" condition in Figure 19) and the full, post-effort first-hand and empathy for pain task afterwards. This structure was purposefully chosen to avoid first-hand pain experience before the prosocial effort task and to measure downregulating effects of the placebo on empathy early vs. late in the session.

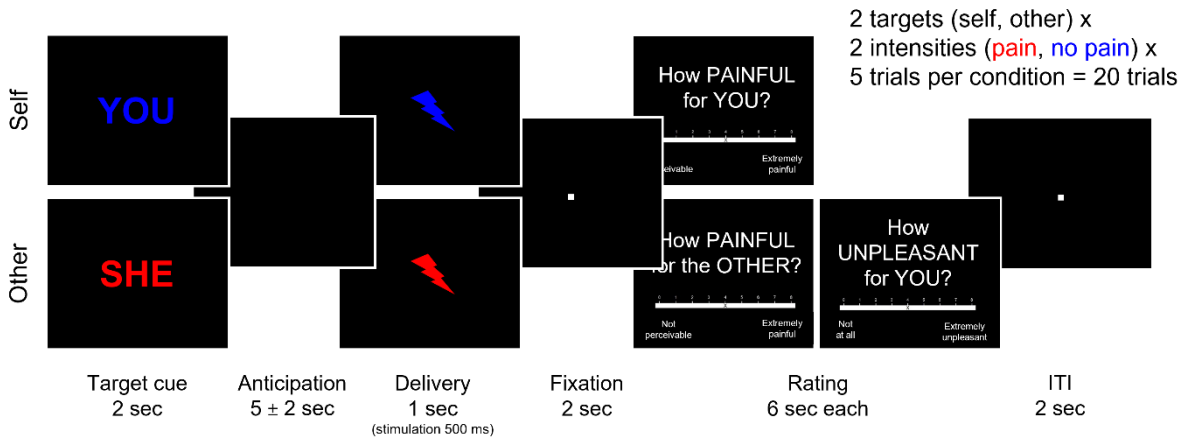

Figure 19. Participants completed measures of empathy for pain before and after the prosocial effort task. Post-effort, the participants either received electrical stimulation themselves (Self) or observed the second participant seemingly receiving such stimulation (Other). Afterwards, participants were asked to rate the pain intensity and unpleasantness of these stimulations. Pre-effort, participants only supplied empathy ratings and did not receive first-hand stimulation. Figure taken from Hartmann et al. (2022).

Post-experimental questions. At the end of the session, we assessed any doubts regarding the cover story (whether participants believed their anonymity was kept, whether their decisions were kept secret from the other participant, and whether they felt their decisions were monitored by the experimenters) and the placebo manipulation to identify non-responders (section Participants in the Supplement). We also measured how painful they remembered the average painful and non-painful stimulation in the pain task.

Participants

Participants were German-speaking, right-handed young university students with normal or corrected-to-normal vision who reported no history of neurological or psychiatric disorders. Our sample had the final preregistered size of $N = 90$ participants (45 participants

per group). We based our group sizes on previous studies using similar versions of the effort task (Crockett et al., 2015; Lockwood, Hamonet, et al., 2017). All exclusion criteria were determined *a priori* in the preregistration. Placebo analgesia non-responders were determined as in Rütgen, Seidel, Silani, et al. (2015; Supplement for more information): First, we recorded verbally expressed doubts about the analgesic effects of the pill or the cover story. Second, differences of the belief scores about the effectiveness of the placebo before and after the induction procedure were analyzed. Third, we took the number of conditioning trials needed to suggest pain relief into account. Dropouts and exclusions in each group were replaced until the group sizes of 45 were reached. These exclusion criteria were not related in any way to our two outcomes of interest, empathy for pain and prosocial behavior, but served to establish a reliable first-hand placebo analgesia effect as a prerequisite for the group comparisons. The two final groups were comparable regarding age and trait measures of socio-cognitive and emotional abilities (Table 32 in the Supplement).

Data collection and analysis

Tasks were implemented in Cogent 2000 Version 1.33 running in MATLAB R2018a (Mathworks, 2018). Data were processed and analyzed using MATLAB R2016a and RStudio 4.1.0 (2021-05-18; R Core Team, 2020). All p values were interpreted two-sided. Wherever Mauchly's Test for Sphericity was violated, we report p values using Greenhouse-Geisser correction (^{GG}). The manuscript was checked for statistical reporting errors using statcheck (Rife et al., 2016) and for reference errors using reciteworks (4cite Labs).

Manipulation checks

We conducted five manipulation checks, some of which were preregistered and others were added post hoc due to the novelty of the design, as indicated below: First, we evaluated the correct performance of the prosocial effort task (1) and the cover story in both groups (2) (see Supplement). Then we tested the effectiveness of the placebo analgesia induction

procedure (3-5): The placebo groups' belief in the effectiveness of the medication (3) was analyzed by calculating three paired t-tests comparing two of the three time points (pre-conditioning/post-conditioning/post-session). While these analyses were preregistered as "exploratory", they were also employed in our previous studies using a very similar placebo analgesia induction with a gel instead of a pill (Hartmann, Riva, et al., 2021; Hartmann, Rütgen, Riva, et al., 2021). Based on these studies, we expected a strong belief in the medication and an increased belief from pre- to post-conditioning (Supplement for exact criteria). (4) We aimed to evaluate whether the placebo analgesia induction influenced a) first-hand pain as well as b) other-related pain intensity and unpleasantness ratings with the goal of replicating the placebo analgesia effect reported in Rütgen, Seidel, Silani, et al. (2015). As in that study, we expected placebo analgesia to downregulate participants' first-hand pain as well as their pain empathy. We thus preregistered that placebo analgesia would lead to lowered empathic responses. We calculated two ANOVAs using the pre-effort empathy ratings, with the other pain intensity or the unpleasantness ratings as the dependent variables, and the independent variables *treatment* (placebo/control) and *intensity* (pain/no pain). We then calculated an additional two ANOVAs using the post-effort first-hand and empathy for pain ratings: the first ANOVA compared the self- and other-related pain intensity ratings on the independent variables *treatment* (placebo/control), *target* (self/other) and *intensity* (pain/no pain); the second ANOVA compared the unpleasantness ratings on *treatment* (placebo/control) and *intensity* (pain/no pain). The pre-effort empathy for pain analyses were not preregistered but mirrored the preregistered post-effort ones. (5) To measure whether the placebo effect lasted until the end of the session, we compared the post-experimental rating about how much pain was felt on average in the pain task using a t-test, using the index of pain – no pain ratings as the dependent variable and *group*

(placebo/control) as a factor. This check had not been preregistered, but was also employed in our previous studies (Hartmann, Riva, et al., 2021; Hartmann, Rütgen, Riva, et al., 2021).

Preregistered core analyses

We calculated a mixed ANOVA with the 'proportion of work offers chosen' as the dependent variable, and the factors *effort level* (1-5), *shock reduction / helping* (1-5) and *group* (placebo/control) as independent variables. We then repeated this analysis with reaction time as the dependent variable. Lastly, we ran a LMM with area under the curve (AUC) of the force data as the dependent variable and group, effort level, shock reduction and their interactions as fixed effects, and included a subject-level random intercept (as well as exploratory mixed models for the single trial choice and RT data). To check whether placebo analgesia influenced general motivation, we calculated a t-test to compare the two groups on the MVC and exerted force in the one-shot self-trial.

Post hoc analyses

To evaluate the effects of the placebo induction on participant's general strength and mood, we calculated three ANOVA with the dependent variables MVC, positive or negative mood, with *time* (pre-induction/post-induction/post-session) and *group* (placebo/control) as factors. We also investigated correlations between the two tasks, i.e., empathy for pain and prosocial behavior. To this end, we correlated the first-hand pain, other-related pain intensity and unpleasantness ratings in the first-hand and empathy for pain task with the proportion of prosocial choices in the prosocial effort task. Moreover, we explored associations between prosocial choices and reaction time in the prosocial effort task. Lastly, individuals differ in how much they value other people's rewards relative to their own (prosocial/altruistic vs. individualistic oriented). We explored the relationship between prosocial choices in the prosocial effort task and social value orientation (SVO) by correlating the proportion of prosocial choices to each participants' social value angle from the SVO by Murphy et al.

(2011), which was calculated as the arc tangent of the ratio for other- vs. self-related payoffs as an angle in degrees (with higher values meaning higher prosocial/other-related orientation). All of these correlations were not preregistered and are therefore exploratory and reported uncorrected for multiple comparisons.

4.2.5 Results

Both groups show correct task performance, cover story belief as well as similar strength, motivation, and mood

There were no significant group differences regarding correct performance of the prosocial effort task and believability of the cover story (manipulation checks 1 and 2; Figure 23 and Tables 33-35 in the Supplement for details). We also did not observe any group or time differences in participants' general strength measured as MVCs over the course of the session (all $p > .561$; Figure 24 and Table 36 in the Supplement). In the analysis of participants' effort exertion when aiming to win an additional monetary bonus for themselves, we observed no group differences, neither in participant's MVC ($p = .432$) nor in the AUC of the exerted force ($p = .175$; Figure 25A for MVC and Figure 25B for force data). Evaluating the participants' mood at three time points over the whole session, we observed that both positive and negative mood decreased significantly over the course of the session (both p's < .001), but these effects were similar for both groups (Figure 26A for positive, Figure 26B for negative mood, and Tables 37 and 38 in the Supplement).

Placebo vs. control group differ in first-hand pain but not in other-related pain intensity or unpleasantness ratings

In assessing the placebo analgesia effect, we observed a significant increase in the belief about the effectiveness of the pill in the placebo group from pre- to post conditioning ($t(44) = 3.92$, $p < .001$, mean of the differences (M_{diff}) = 13.58, 95% CI [6.59, 20.57], Cohen's $d_z = 0.58$; pre-conditioning: $M \pm SEM = 65.44 \pm 3.24$; post-conditioning: 79.02 ± 2.21; manipulation check 3; Figure 20A). From post-conditioning to post-session (67.27 ± 3.71),

the belief ratings decreased significantly ($t(44)$ = -4.05, p < .001, M_{diff} = -11.76, 95% CI [-17.60, -5.91], Cohen's d_z = 0.60), while the post-session ratings did not differ significantly from the ones measured pre-conditioning ($t(44)$ = 0.34, p = .735, M_{diff} = 1.82, 95% CI [-8.97, 12.62], Cohen's d_z = 0.05). Importantly, the average belief rating was generally very high ($M \pm SEM$ = 70.58 ± 2.06 on a scale from 0-100), indicating a generally high belief in the medication's effectiveness.

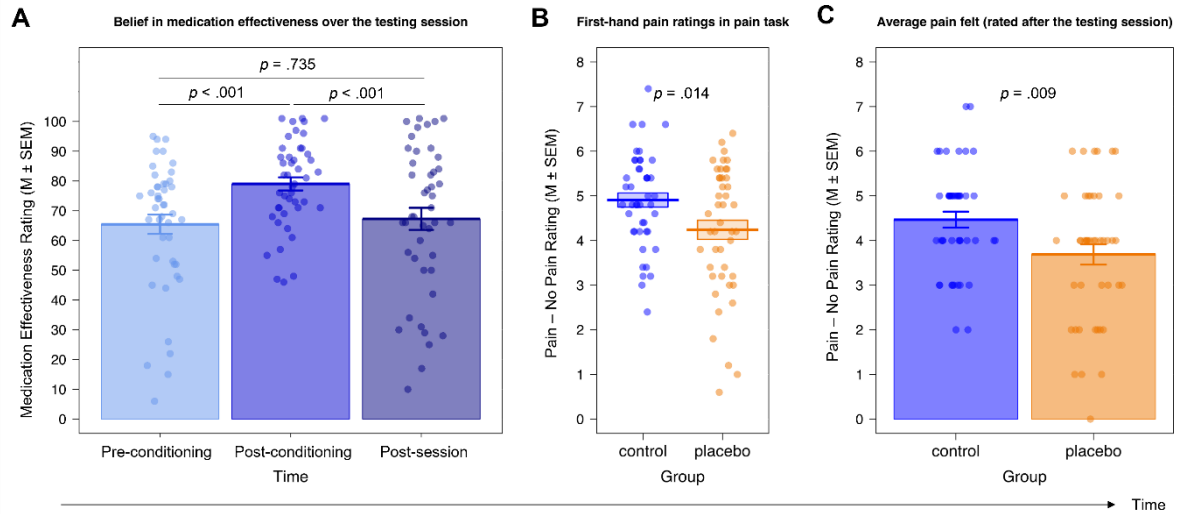

Figure 20. Manipulation checks 3, 4 and 5 evaluating the first-hand placebo analgesia effect. A) We observed high belief ratings in general and a significant increase in the belief in the effectiveness of the medication from before to after the conditioning procedure. Although this belief significantly decreased towards the end of the session, it did not drop lower than the initial belief before the conditioning. B) In the first-hand and empathy for pain task, participants of the placebo group rated the electrical stimulation they received on the back of their hand as significantly less painful compared to the control group. C) Finally, participants in the placebo group indicated even at the end of the session that they remembered the stimulations in the first-hand and empathy for pain task to be significantly less painful compared to participants in the control group. Figure taken from Hartmann et al. (2022).

Next, we analysed the pre- and post-effort ratings in our first-hand and empathy for pain task (manipulation check 4; Figure 20B for first-hand pain, Figure 21 for other-related pain intensity and unpleasantness, Supplement for more detailed results). Analyses confirmed a significant placebo effect for first-hand pain, as shown by general lower ratings in the placebo compared to the control group (main effect of group, p = .008) independent of intensity or target as well as a bigger rating difference in the index (pain – no pain stimulation) between self- and other-related stimulation (i.e., control ($self_{pain - no\ pain}$ - $other_{pain - no\ pain}$) > placebo ($self_{pain - no\ pain}$ - $other_{pain - no\ pain}$)) for the control compared to the placebo

group (group x intensity x target interaction, p = .020), but no group differences regarding other pain intensity or unpleasantness ratings (p's > .128), neither in the pre- nor post-effort pain task data.

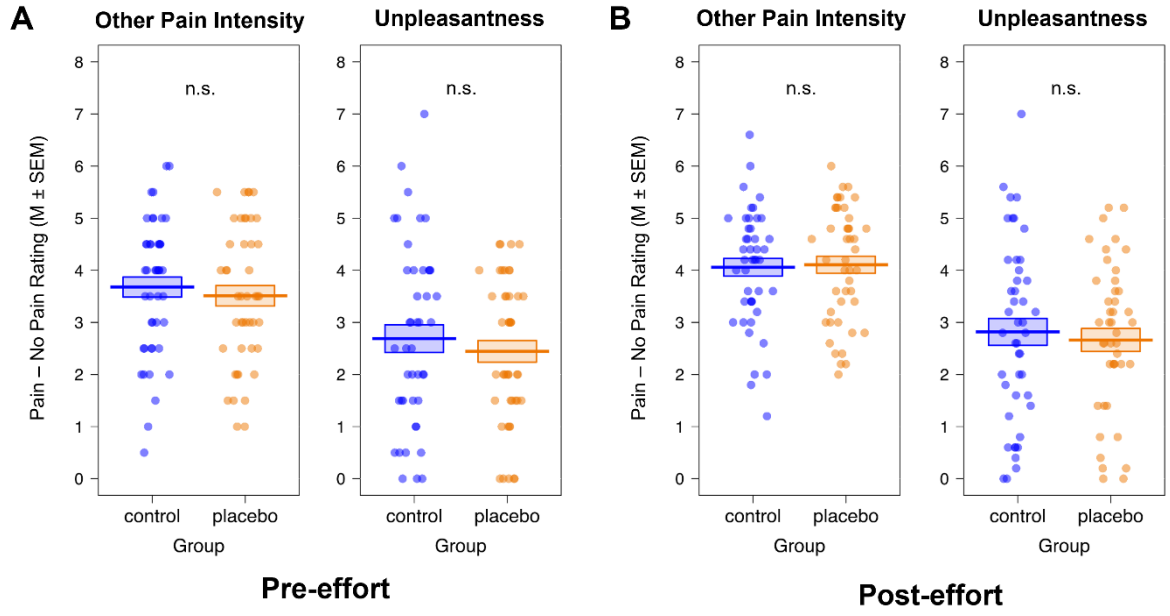

Figure 21. Manipulation check 4 evaluating the effect of placebo analgesia on other pain intensity and unpleasantness ratings. Participants completed A) pre-effort empathy for pain task (Tables 39 and 40 in the Supplement) and B) the full post-effort first-hand and empathy for pain task afterwards (Tables 41 and 42 in the Supplement). They rated pain intensity as well as their own unpleasantness when the other participant (allegedly) received electrical stimulation in both instances. We observed no effect of placebo analgesia on other pain intensity or unpleasantness, neither in the pre- nor in the post-effort data. Figure taken from Hartmann et al. (2022).

While the hypothesized group differences in other pain intensity and unpleasantness ratings went into the expected direction (placebo < control), they were not significant, and their effect sizes (Cohen's d's between 0.04 and 0.15) were much smaller compared to previous studies that had also used a between-subjects design and very similar setup (e.g., Rütgen, Seidel, Silani, et al., 2015, Cohen's d's of first-hand analgesia effect between 0.62 and 0.79, and empathy analgesia effect between 0.44 and 0.76). We further observed a significant difference between the average index for first-hand pain – no pain ratings in the task when asked to remember the pain at the end of the session (t(83.12) = 2.68, p = .009, 95% CI [-0.20, 1.36], Cohen's d = 0.57; manipulation check 5; Figure 20C). In this context,

the placebo group (3.69 ± 0.23) remembered the self-directed electrical stimulation as significantly less painful compared to the control group (4.47 ± 0.18).

Taken together, manipulation checks 3-5 showed the success of the placebo analgesia induction. Replicating previous studies, placebo analgesia downregulated first-hand pain ratings in the placebo compared to the control group, and this effect lasted until the end of the session and thus beyond the part in which the prosocial effort task was performed. Contrary to previous research and our preregistered hypothesis, other pain intensity and unpleasantness ratings did not seem to be affected by the placebo analgesia manipulation, neither when measured directly after the placebo analgesia manipulation nor in the ratings given after the prosocial effort part of the experiment.

Placebo group displays reduced prosocial behavior compared to the control group in their choices, reaction times, and exerted force

In the ANOVA analyzing the proportion of work offers chosen (Figure 22 here and Table 43 in the Supplement) we observed a main effect of effort level ($F(4,352) = 60.06$, $p^{GG} < .001$, $\hat{\eta}_G^2 = .13$), showing that participants chose the work option less often the more effort they were asked to exert, and this was independent of the shock reduction for the other and the group (effort level 1: 0.97 ± 0.01; effort level 2: 0.95 ± 0.01; effort level 3: 0.90 ± 0.01; effort level 4: 0.80 ± 0.02; effort level 5: 0.69 ± 0.02). We also observed a main effect of shock reduction ($F(4,352) = 63.12$, $p < .001^{GG}$, $\hat{\eta}_G^2 = .09$), showing that participants chose the work option more often the more shocks they could prevent for the other person, independent of the effort level or group (preventing 5 shocks: 0.94 ± 0.01; preventing 4 shocks: 0.91 ± 0.01; preventing 3 shocks: 0.89 ± 0.01; preventing 2 shocks: 0.84 ± 0.02; preventing 1 shock: 0.71 ± 0.02). Both of these effects were expected from previous studies and predicted by our preregistered, directional hypotheses, while any interactions were left exploratory. Intriguingly, we observed a group x shock reduction interaction ($F(4,352) = 4.10$, $p = .020^{GG}$,

$\hat{\eta}_G^2$ = .01), showing that the placebo group showed reduced prosocial behavior compared to the control group, dependent on the number of shocks the other would receive, but independent of effort level (Figure 22A). Post hoc tests confirmed that this group difference was true only for a shock reduction of 1, i.e., the lowest helping level (p < .001, value adjusted using Tukey). Lastly, we observed an effort level x shock reduction interaction (F(16,1408) = 13.11, p < .001^{GG}, $\hat{\eta}_G^2$ = .03), whereby the differences in the proportion of prosocial choices between the five effort levels increased with decreasing possibility to help, independent of group (Figure 22B). In other words, participants differentiated their helping behavior less at the effort levels when they could help more compared to less. No other effects were significant. The generalized LMM of the same data largely mirrored the ANOVA results (Table 44 in the Supplement). The same ANOVA analyzing reaction time during the choice phase revealed faster RTs for choices involving lower effort exertion as well as higher possibility to help over both groups (Table 45 in the Supplement). In other words, participants were faster in their decisions when they needed to put in less effort and could help more. Furthermore, we observed an effort level x shock reduction interaction, whereby the differences in RTs between the five effort levels decreased with increasing possibility to help, independent of group (all p's < .001). Regarding our preregistered hypotheses, no other effects were significant, showing no group differences in the choice RTs. The LMM of the same data mirrored the ANOVA results, except for an additional main effect of group (p = .046), whereby the placebo group was slower to make their decisions compare to the control group, independent of effort level or shock reduction (Table 46 in the Supplement). In the LMM analyzing the exerted force (Table 47 in the Supplement), we found a main effect of group ($\chi^2_{(1)}$ = 3.99, p = .046), whereby the placebo group (0.43 ± 0.002) exerted less force compared to the control group (0.44 ± 0.002), after having chosen to put in effort to help the other. Moreover, we again observed main effects of effort ($\chi^2_{(4)}$ =

29424.90, $p < .001$) and shock reduction ($\chi^2_{(4)} = 9.99$, $p = .040$), showing that participants exerted more force with increasing effort level and increasing shock reduction / possibility to help. We additionally found an effort x shock reduction interaction ($\chi^2_{(16)} = 140.12$, $p < .001$).

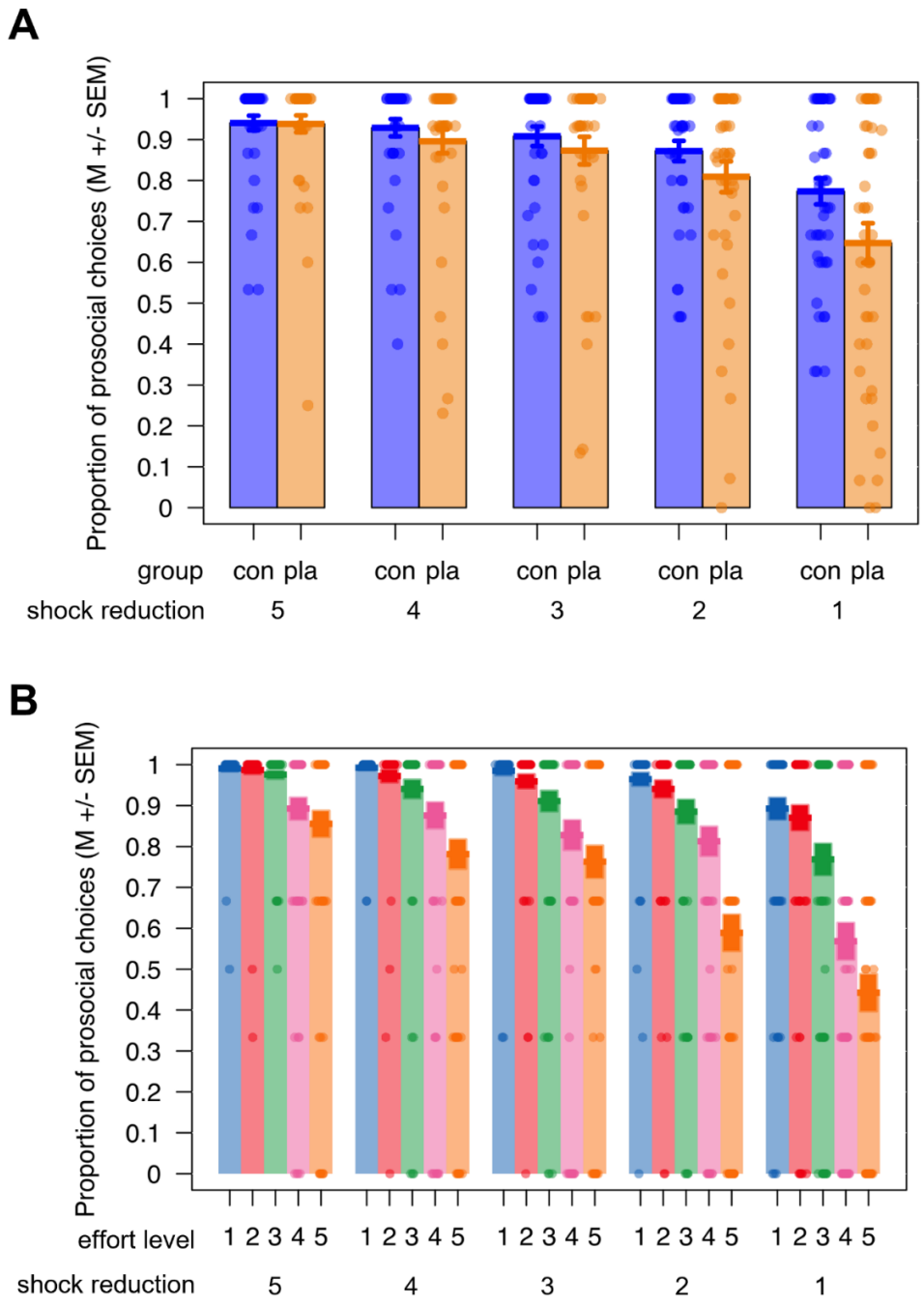

Figure 22. A) Participants of the placebo group (orange) chose the prosocial option significantly less often compared to the control group (blue) when the possibility to help was highest, i.e., a reduction of 5 shocks, while the groups did not differ for the other shock reduction amounts (reduction of 1-4 shocks; group x shock reduction interaction). B) Participants differentiated their helping behavior less over the five effort levels when they could help more compared to less (effort level x shock reduction interaction). Figure taken from Hartmann et al. (2022).

Prosocial behavior correlates with choice reaction times and unpleasantness but not pain intensity when observing others' pain

We observed a significant positive association between the amount of prosocial choices and unpleasantness ratings across all participants (Spearman's ρ = .22, p = .035), whereby higher levels of unpleasantness were associated with increased prosocial behavior (choosing the prosocial option more often; Figure 27A in the Supplement). We did not find a significant association between prosocial behavior and first-hand pain (ρ = .03, p = .768) or other pain intensity ratings (ρ = .01, p = .920; Figure 27B in the Supplement). Moreover, we found a significant negative correlation between participants' reaction times when making their choice and the proportion of prosocial choices in the prosocial effort task (ρ = -.58, p < .001), showing that faster reaction times were associated to increased prosociality, and vice versa (Figure 27C in the Supplement). Lastly, there was a significant positive correlation between participants' trait SVO and their prosocial behavior in the prosocial effort task (ρ = .23, p = .028), showing that participants who ascribed themselves to be more other-oriented also had a higher proportion of prosocial choices, or vice versa (Figure 27D in the Supplement).

4.2.6 Discussion

We investigated the causal effects of a placebo painkiller on prosociality. Participants under placebo analgesia showed reduced willingness to put in effort to help others, slower reaction times when deciding to help, and exerted less force when putting in effort to help.

The placebo group was slower when deciding whether to help compared to controls. In a similar task, Crockett et al. (2015) related slower response times to more deliberative moral decision-making. This matches the reduced willingness to make prosocial choices in our study and suggests a shift to more deliberative decisions: The placebo group might have taken longer in deciding because, rather than helping automatically, they more carefully evaluated the extent to which helping would be beneficial. However, as earlier studies linked opioid use to prolonged reaction times (Banning & Sjøgren, 1990; Banning et al., 1992),

future research should replicate this finding and assess its specificity for social behavior. Higher proportion of prosocial choices was also associated with faster reaction times. This could indicate that prosocially-oriented people make such decisions faster and is in line with studies associating quicker decisions to greater prosociality (Chen & Krajbich, 2018; Rand et al., 2012).

Even when having chosen to help, the placebo group exerted less energy compared to controls. Lockwood, Hamonet, et al. (2017) reported similar findings when participants exerted effort for others compared to themselves. Thus, our results suggest that placebo analgesia could exacerbate 'prosocial apathy'. As the opioidergic system was shown to regulate (hedonic) reward processing and social motivation (Chelnokova et al., 2014; Scott et al., 2007), effects of placebo analgesia on prosociality could be explained in terms of a general reduction of reward-seeking motivation. Importantly, we observed no group differences in our control measures of strength, motivation, or mood, suggesting that our manipulation affected social motivation selectively.

Although placebo analgesia successfully reduced first-hand pain sensitivity, we did not replicate previous studies of reduced other-related pain intensity and unpleasantness (Mischkowski et al., 2016; Rütgen, Seidel, Riečanský, et al., 2015; Rütgen, Seidel, Silani, et al., 2015; Vecchio & De Pascalis, 2021). One explanation for this discrepancy could be that our placebo induction was not strong enough to affect empathy for pain. What speaks against this is that we found no group differences in empathy for pain measured directly after the induction and showed that the first-hand placebo response lasted until the end of the session (~2 hours post-induction). However, there were several differences between our and previous studies reporting placebo or painkiller effects on empathy, e.g., anonymity of participants towards each other, varying study doctors in each session, and framing (the focus being on the prosocial effort task here and on the pain task in previous studies), which could all have

influenced the way placebo analgesia affects pain empathy. Our results thus highlight that altering first-hand pain may influence prosociality via mechanisms beyond empathy and affect sharing, such as perspective taking (Decety, 2021) or the use of cognitive strategies (e.g., reappraisal, Lockwood et al., 2014). Whether placebo analgesia influences helping via different routes and how perception ("what we feel") is linked to actions ("what we do") are interesting avenues for future work.

Unpleasantness ratings when observing others in pain are usually seen a marker of affect sharing, while pain intensity ratings are thought to measure cognitive-evaluative components of empathy (Lamm & Majdandžić, 2015 for a review). Interestingly, we found that the proportion of prosocial choices was positively associated with higher unpleasantness ratings when observing others in pain, but not with self- or other-related pain intensity ratings. This supports previous work linking empathy and prosociality (Eisenberg & Fabes, 1990 for a review; Lockwood et al., 2016). For example, Hein et al. (2010) found that self-reported empathic concern for another's suffering predicted later costly helping (enduring physical pain to reduce the other's pain). However, Gallo et al. (2018) stressed a connection between ratings of the pain intensity observed in others and subsequent donation behavior to reduce their pain, highlighting the role of cognitive-evaluative perception of another's pain. These findings raise the argument that some aspects of the empathic response influence different types of prosociality (e.g., putting in effort, enduring pain yourself, donating money) in different ways. To tease apart these differences, future studies could connect different ways to measure empathy with different ways to measure prosociality.

The present study had strengths and limitations worth discussing. We preregistered our study, clearly distinguishing confirmatory from exploratory findings and reducing the risk of type-I errors (Nosek et al., 2018). We took great care in excluding alternative explanations such as social norms, reciprocity, or reputation, as participants never met face-to-face

(Crockett et al., 2015). Belief in our cover story highlighted that participants' prosocial behavior was likely not influenced by these concerns. Anonymity may still have reduced empathic responses, possibly through mechanisms such as objectification (Eklund, 2006), dehumanization (Cameron et al., 2015), or distancing (Cameron et al., 2019; Story et al., 2020). However, such effects would likely be independent of the placebo manipulation.

As in Lockwood et al. (2021), we operationalized prosocial behavior using costly choices and exertion of physical effort, and kept this behavior independent of monetary gains, group allocation or study time. This task setup grasped both peoples' explicit choice behavior as well as the implicit energization of their actions, disentangling 'true' from 'superficial' helping behaviors. In doing so, we aimed to measure prosocial behavior in an ecologically more valid way considering situation-specific factors, which may better translate to real-world prosocial acts. By incorporating different levels of shock reduction, our design also revealed that placebo participants' drop in helping behavior scaled with the amount of shock reductions they could attain: While helping behavior most strongly differed in low-helping conditions, it was virtually identical for maximum shock reduction. This speaks for a modulatory effect of placebo analgesia: If there is high need for and effectiveness of helping, the incentive to help may be so high that placebo analgesia is not able to modulate behavior; conversely, if stakes are lower, placebo analgesia has leverage to exert its effects.

Finally, the proportion of prosocial choices correlated with increased prosocial tendencies in trait social value orientation (SVO). This nicely links prosocial traits people ascribe to themselves with their actual behavior, complementing past studies demonstrating that the level of cooperativeness in SVO relates to contributing more hours for a prosocial cause (McClintock & Allison, 1989) and greater donations (Van Lange et al., 2010).

These strengths notwithstanding, future research is required to translate our laboratory-based findings to measures of prosociality in real-life, e.g., using ecological momentary

assessment or diary studies (Morelli et al., 2014; Rameson et al., 2012). And although the present study gives insights into effects of altered pain sensitivity on our social emotions and behavior, generalizations to people affected by pain-related disorders and chronic painkiller use will require different study designs and participants.

In sum, placebo analgesia decreased people's willingness to exert effort to reduce others' pain. Therefore, manipulating one's own pain sensitivity changes not only how we experience pain but also affects our decisions to help others. Notwithstanding independent validation and extension to more ecological settings, and in particular to (ab)use of painkillers, this has important implications for the social interactions of people under the influence of analgesics and those with chronic pain conditions.

4.2.7 Acknowledgements

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4.2.8 CRediT author statement

Helena Hartmann: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Software, Visualization, Writing - original draft, Writing - review & editing. **Paul Forbes:** Conceptualization, Formal analysis, Methodology, Supervision, Writing - original draft, Writing - review & editing. **Markus Rütgen:** Conceptualization, Formal analysis, Methodology, Supervision, Writing - original draft, Writing - review & editing. **Claus Lamm:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing - original draft, Writing - review & editing.

4.2.9 Funding

The present study was financially supported by the uni:docs scholarship of the University of Vienna, the Marietta-Blau scholarship of the Agency for Education and Internationalisation Austria (OeaD) (both awarded to H.H.), the Austrian Science Fund (FWF W1262-B29), and the Vienna Science and Technology Fund (WWTF VRG13-007). None of the funders had any role in study design, data collection and analysis, interpretation, writing or decision to publish.

4.2.10 Declarations of Interest

H.H. works as a researcher and psychologist for MyMind GmbH, a company developing a neurofeedback training game for children with autism spectrum disorder and attention deficit hyperactivity disorder, but this work is in no way related to the present research. The remaining authors declare that they have no financial interests or potential conflicts of interest.

4.2.11 Supplement

Procedure

Eligible participants were sent trait questionnaires to be completed online prior to coming to the lab. They were asked to abstain from alcohol, drugs, and any medication intake (except oral contraceptives) 24 hours before the experiment and to abstain from smoking, food, caffeine, and any drinks other than water one hour before the experiment. This was done to increase homogeneity of testing conditions.

During the **role assignment** procedure, the participant and the confederate were positioned on either side of a door and simultaneously each drew a ball from a box. Importantly, the two participants never met face to face, but arrived (and supposedly left) at staggered times. Both participants wore gloves during the procedure to conceal each other's identities (e.g., age, race, etc.). They were further instructed not to speak and direct their gaze

away from the box when drawing their ball. To keep up the cover story, both were asked to wave to each other once, otherwise they did not interact with each other. Since this study investigated prosocial behavior, the real participant was always be assigned the role of "Decider" and the confederate always the role of "Receiver", independent of the colour of the ball they drew.

In the **pain calibration**, we gave short-lasting electrical stimulations in multiple trials, moving up stepwise from a rating of 0 = 'not perceivable' until the stimulus was rated as 8 = 'extremely painful but bearable' (beginning at a low intensity of 0.05 mA, step size individually chosen for each participant, so that each rating was experienced at least once). This was then repeated a second time with a small break in between to avoid habituation/sensitization and followed by varying (seemingly "random") stimulation in the before calibrated rating range from 1 to 8. On average, input intensities for the first-hand and empathy for pain task were 0.77 ± 1.15 (*M* ± *SD*) mA (range from 0.09 – 9.00 mA) for painful and 0.10 ± 0.07 mA (range from 0.01 – 0.50 mA) for non-painful stimulation.

In the **effort calibration**, participants gripped the hand dynamometer two times in a row for three seconds, while seeing live feedback of their exerted effort on the screen. They were instructed to hold the device in a certain way (lower arm and hand on a cushion on the table, dorsum of the hand directed towards the table) and asked to maintain this position during all tasks involving the grip force device. This was done to keep the MVC constant (as it can be affected by different holding positions of the dynamometer). During the first calibration, the participants were watched by an experimenter to check for correct execution and corrected if needed, e.g., to press stronger next time or hold the device differently. Participants were urged to press as strongly as they could each time. The maximum of four MVC trials (two before and two after the placebo induction) was taken to calculate the effort levels in the prosocial effort task. As part of the three effort calibrations and to make sure that the effort

levels (effort levels 1-5 corresponding to 30, 40, 50, 60 and 70 % of their MVC, respectively) were perceived similarly in both groups, and that this perception did not change over time, participants completed two items from the NASA Task Load Index (Hart & Staveland, 1988; Effort: "How hard did you have to work to accomplish your level of performance?"; Physical Demand: "How physically demanding was the task?") and one additional question (Unpleasantness: "How unpleasant was it for you?") for each of the five effort levels (on a scale from 1 = not at all to 20 = extremely effortful/physically demanding/unpleasant).

In the **belief ratings** measured only in the placebo group, we asked "How effective do you currently consider the pain medication to be in reducing your pain later during the tasks?". The Positive and Negative Affect Schedule (PANAS; Krohne et al., 1996) included 10 adjectives each for positive and negative mood, answered on a scale from 1 = Little or not at all to 5 = Extremely.

The placebo **conditioning** procedure involved the participants receiving electrical stimulation on the same hand using the exact electrode location as during calibration. These conditioning trials were repeated for a minimum of two and up to a maximum of four times until the subject did not respond with values higher than 5 to the conditioning stimulus, i.e., until it was believable that a pain reduction had taken place. In fact, the pill was a placebo and did not contain any active analgesic or pain-reducing components, but a natural sugar-alcohol (Mannitolum, 40G per pill). The control group did not receive a pill or any type of induction but had waiting times throughout the experiment to keep the session length constant between the two groups. To measure the strength of the placebo effect, we evaluated the participants' belief in the effectiveness of the medication at three time points during the session: directly after the placebo administration (= pre-conditioning), after the placebo induction procedure (= post-conditioning) and after the completion of all tasks (= post-session). Each time, participants indicated how effective they believed the pill to be in

reducing their pain in the tasks on a continuous visual analogue scale (VAS) from 0 = not effective at all to 100 = extremely effective. We then used the first-hand pain ratings in the first-hand and empathy for pain task as a main indication for the placebo effect. Finally, in the post-experimental questionnaires, we asked participants how painful the electrical stimulation had felt in the first-hand and empathy for pain task, to assess whether the belief in the pill lasted until the end of the session.

During all **tasks**, the cover story was kept up by interacting equally with the participant and the confederate, e.g., by coordinating the simultaneous starting of the tasks between the two experimenters and "waiting for the others to be ready" before continuing with the next step. Participants completed all tasks sitting in a room separated from the confederate. All participants completed a prosocial effort task and a first-hand and empathy for pain task on a computer in a fixed order. Afterwards, participants completed a third task unrelated to this project. To keep anonymity, participants were told that they arrived a few minutes apart from each other, saw only each other's gloved hands during the role assignment and left separately at different time points.

In the **prosocial effort task**, all trials were the same length independent of the choices the participant made. Participants completed three blocks of 25 trials each, with breaks of 60s in between. Blocks of the prosocial effort task were pseudorandomized, but trials within a block were kept constant over all participants. All participants exerted the effort with their right hand and made the choices with two fingers of their left hand placed on a keyboard. As part of the cover story, participants were told that the shocks the other person received because of their choices were always "very painful".

The **first-hand and empathy for pain task** was included as a manipulation check for evaluating analgesic effects on first-hand and empathy for pain, to then measure effects of this manipulation on prosocial behavior. Our task differed from the one used in Rütgen,

Seidel, Silani, et al. (2015) in three aspects: (1) We included 20 instead of 60 trials, but collected the same amount of ratings; (2) We did not show pictures of the confederate's face in pain as this would have interfered with the anonymity of participants; (3) we displayed "SHE"/"HE" or "YOU" in big letters instead of arrows as cues to reduce ambiguity about the target of stimulation. However, since this task was completed relatively late in the experiment in relation to the placebo induction, placebo effects could have been reduced compared to the beginning of the experiment. To counteract this, we assessed analgesic effects on empathy for pain at two time points, before (pre-effort) and after (post-effort) the prosocial effort task and used a thorough procedure for identifying non-responders to the manipulation. Twenty trials of the first-hand and empathy for pain task were shown in a pseudorandomized order (four sequences were created manually for each task and alternated over all participants in an a-priori defined order, however, the pre-effort **empathy for pain task** involved only four trials of other-related electrical stimulation (2x pain, 2x no pain) and the first-hand and empathy for pain task started with four non-random other-related stimuli and was followed by the rest of the conditions in the previously specified pseudorandom order). The ratings targeted two different aspects of empathy: (1) Rating of the own subjective degree of unpleasantness when seeing another person in pain ('other unpleasantness'), tapping into affective sharing and vicarious distress; and (2) rating of the intensity of the pain felt by the other ('other pain') as a more cognitive-evaluative aspect of empathy (Lamm & Majdandžić, 2015). For first-hand stimulation, we asked participants to evaluate: 'How painful was this stimulation for you?'; for stimulation of the other person, we asked: 'How unpleasant did it feel for you when the other person was stimulated?' as well as 'How painful was this stimulation for the other person?' (all ratings were given on a 9-point rating scale from 0 = 'not noticeable' to 8 = 'extremely painful/unpleasant'). In the empathy condition, the two subjective rating questions

regarding pain and unpleasantness were presented in a truly random order for each trial and each participant.

The session ended with **follow-up questions**, where we also assessed any doubts that participants had regarding the study setup. Participants answered the questions about their anonymity ("My anonymity in relation to the other participant was kept") and secrecy of decisions ("My decisions were kept secret from the other participant") on a 5-point Likert scale from 1 = Do not agree at all to 5 = Agree completely, i.e., higher values meaning higher agreement with the statement. The monitoring question ("How often did you have the feeling that your decisions were generally 'monitored'?") was answered on a 5-point Likert scale from 1 = never to 5 = very often, with higher values indicating higher frequency. The whole experiment lasted approximately three hours. Participants were told that they would receive a compensation of 10€ per hour plus a bonus in one of the tasks for their participation. In reality, everybody received a total compensation of 35€. A pilot study with nine subjects was conducted before the start of data collection and prior to the upload of the preregistration to test the study procedure, especially for the placebo group. This pilot data was not used in the final analysis and is thus not reported in the present manuscript.

Participants

Each participant was screened for exclusion criteria using an online questionnaire hosted on SoSciSurvey (Leiner, 2019), with the link sent via email. **Exclusion criteria** were a past or present enrolment in academic studies including psychology, pharmaceutics or medicine (veterinary, dental, human, etc.) as well as other medical-related trainings (e.g. nurse), any neurological or psychiatric conditions, past or present substance abuse (alcohol daily use, drugs weekly or daily use), the intake of psychopharmacological medication (besides oral contraceptives) within the last three months, and past participation in at least one placebo study or a study involving similar deceptive elements. Furthermore, participants above the

clinical cut-offs of the following questionnaires were excluded: Beck's Depression Inventory II (BDI-II; cut-off = 14; Kühner et al., 2007); Autism Quotient (AQ-k; cut-off = 17; Freitag et al., 2015); Toronto Alexithymia Scale (TAS-20; cut-off = 51; Bach et al., 1996; Table 32). Once deemed eligible, participants were pseudo-randomly allocated to either the placebo or control group. A document with subject codes and group allocation was created beforehand, where placebo and control sessions were alternated (01 = control, 02 = placebo, 03 = control, etc.). Participants with choices reflecting disengagement from the prosocial effort task, like choosing the baseline rest option in 100% of all trials (i.e., never exerting effort), having more than 10% of fail trials or failing to exert effort due to fatigue after some time, were excluded.

Regarding the **non-responder criteria**, if a participant expressed doubts about the cover story, we asked them to elaborate these further and participants with strong doubts were excluded. Exceptionally low total belief scores (sum of pre- and post-conditioning scores lower than 66.6, values can range from 0 to 200) and strong decreases between first and second measure (pre- minus post-conditioning score bigger than 33.3) served as a second measure for lack of responding. Third, we took the number of placebo conditioning trials into account. If participants responded with a value greater than 5 on a 9-point rating scale from 0 = 'not noticeable' to 8 = 'extremely painful, but bearable' to the conditioning stimulus (delivered at a medium intensity of 4), we deemed the conditioning trial as non-successful, waited another few minutes "for the medication to take effect", and then tried again. This was repeated for a maximum of four times or until participants responded with values below 6 to the conditioning stimulus in a trial. If more than three of these trials were necessary, this was taken as an indication of non-responding to the placebo treatment and the participant was excluded from further analysis. Included participants needed an average of $M \pm SD = 2{,}29 \pm$

0.46 (range = 2-3) conditioning trials to respond to the placebo induction and no participant was excluded based on this criterion.

Table 32
Sociodemographic characteristics and trait questionnaire scores of the two groups.

	Placebo group	Control group	$t(df)$	p
N (male/female)*	45 (21/24)	45 (21/24)	---	---
Age*	23.56 ± 2.90	24.00 ± 4.32	0.57(76.95)	.569
Empathic concern (IRI)*	18.47 ± 4.81	18.40 ± 4.76	-0.07(87.99)	.948
Perspective taking (IRI)*	18.78 ± 4.79	18.36 ± 3.99	-0.45(85.21)	.651
Prosocial behavior (HAS)*	78.93 ± 8.90	78.82 ± 9.59	-0.06(87.50)	.955
Behavioral activation (AMI)*	2.60 ± 0.59	2.52 ± 0.68	-0.58(86.71)	.566
Social motivation (AMI)*	2.87 ± 0.61	2.66 ± 0.71	-1.46(86.12)	.149
Emotional sensitivity (AMI)*	2.54 ± 0.63	2.61 ± 0.64	0.53(87.96)	.599
Social Value Orientation (SVO)*	Individualists: n = 10 Prosocials: n = 35 31.95 ± 10.91	Individualists: n = 7 Prosocials: n = 38 32.52 ± 10.65	0.25(87.95)	.803
Psychopathy (SD3)*	18.13 ± 3.89	19.62 ± 5.34	1.51(80.42)	.134
Alexithymia (TAS-20)$^{+}$	38.09 ± 6.76	39.93 ± 6.87	1.28(87.98)	.203
Autism (AQ-k)$^{+}$	6.62 ± 3.74	6.60 ± 2.99	-0.03(83.96)	.975
Depression (BDI-II)$^{+}$	4.24 ± 3.67	4.55 ± 4.07	0.381(87.09)	.704

Note. Data are given as group means or sums ± standard deviations. Group comparisons were done using Welch's two-sample t-tests with group as a between-subjects factor. IRI = Interpersonal Reactivity Index (Davis, 1980; sum); HAS = Helping Attitudes Scale (Nickell, 1998; sum); AMI = Apathy Motivation Index (Ang et al., 2017, average); SVO = Social Value Orientation (reported value calculated as the arc tangent of the ratio for other- vs. self-related payoffs as an angle in degrees; Murphy et al., 2011); SD3 = Short Dark Triad (Jones & Paulhus, 2014; sum); TAS = Toronto Alexithymia Scale (Bagby et al., 1994; total sum); AQ-k = Autism Quotient Short Form (Freitag et al., 2015; sum); BDI-II = Beck Depression Inventory (Kühner et al., 2007; sum). All questionnaires were given in their original German version or were translated to German by the authors. * Scores used for matching the two groups; + Scores used for participant exclusion based on cut-offs (BDI-II cut-off = 14, AQ-k cut-off = 17, TAS-20 cut-off = 51).

In total, we recruited 112 participants, nine of which were excluded for having doubts about the second participant (six in the control group, three in the placebo group), eight because of non-responding to the placebo manipulation (six because of doubts, two because of belief in the medication effectiveness), four because of > 10% of fail trials in the prosocial effort task, and one participant for not performing that task properly. This added up to ~12% of non-responders in the placebo group, which we considered comparable to the range of 8-10% non-responders in our previous work (Rütgen, Seidel, Silani, et al., 2015).

Deviations from the preregistration

We made a mistake in describing the ANOVA with the unpleasantness ratings in the initial preregistration (https://osf.io/g3acp), which was corrected in an amendment (https://osf.io/qw3kg) uploaded during data collection. We had initially preregistered to analyze the force data with an ANOVA (just as the choice and reaction time data), but this was not possible with the ezANOVA function due to missing cells in the design (people did not always choose to exert effort in each trial and thus did not have data for every effort and/or shock reduction level). We therefore calculated an ANOVA of a linear mixed model instead. Moreover, as the two groups were comparable regarding social value orientation and apathy motivation, we refrained from repeating the main analyses of the prosocial effort task (choice, reaction time and force) with social value orientation or apathy motivation as a covariate. Lastly, we did not include computational modelling of the choice data in this paper (these analyses were mentioned as exploratory in our preregistration).

Analyses and results

Data analysis. Cohen's d's were calculated using the effect size calculation spreadsheet (version 4.2) provided by Lakens (2013). For analyses of variance (ANOVAs), we used the function ezANOVA from the R package ez, for Welch's two-sample t-tests, we used the function t.test from the R package stats, for linear mixed models (LMMs), we used the function lmer (or glmer for the binary choice data) from the R package lme4. Follow-up paired comparisons were computed using the Tukey method with the function pairs from the R package emmeans. Spearman's rank correlations were computed using the function cor.test from the R package stats.

NASA ratings. We compared the NASA ratings for effort, unpleasantness, and physical demand (manipulation check 1) of the baseline (no effort exertion, but just holding the grip force device) and the five effort levels using three ANOVAs with the factors *effort level* (1-

6), *time* (pre-induction/post-induction/post-session) and *group* (placebo/control). Participants perceived the effort exertion more effortful, physically demanding, and unpleasant with increasing effort level. Below we report the full results of the ANOVAs of the NASA ratings for effort (Table 33), physical demand (Table 34) and unpleasantness (Table 35) as well as the matching graphs in Figure 23. We observed main effects of effort level in all three ratings, demonstrating that participants perceived the effort exertion more effortful ($F(5,440) = 311.53$, $p^{GG} < .001$, $\hat{\eta}_G^2 = .40$), physically demanding ($F(5,440) = 384.74$, $p^{GG} < .001$, $\hat{\eta}_G^2 = .50$), and unpleasant ($F(5,440) = 183.21$, $p^{GG} < .001$, $\hat{\eta}_G^2 = .32$) with increasing effort level (baseline rest: $M \pm SEM = 4.26 \pm 0.36$; effort level 1: 6.93 ± 0.32; effort level 2: 8.26 ± 0.28; effort level 3: 10.86 ± 0.27; effort level 4: 13.26 ± 0.26; effort level 5: 15.29 ± 0.24). Tukey post hoc contrasts indicated that all three ratings of all effort levels were significantly different from each other (all $p < .039$). Significant main effects of time in all three ratings showed that effort ($F(2,176) = 15.25$, $p^{GG} < .001$, $\hat{\eta}_G^2 = .02$), physical demand ($F(2,176) = 5.15$, $p^{GG} < .001$, $\hat{\eta}_G^2 = .01$), and unpleasantness ($F(2,176) = 4.81$, $p^{GG} = .008$, $\hat{\eta}_G^2 = .01$) were rated differently for the three time points (pre-induction, post-induction, and post-session). Tukey post hoc contrasts indicated that the pre-induction effort ratings (10.62 ± 0.25) were significantly greater compared to the effort ratings post-induction (9.33 ± 0.26, $p = .001$) and post-session (9.48 ± 0.27, $p = .005$). There was a trend ($p = .068$) for lower physical demand ratings post-induction (7.45 ± 0.23) compared to post-session (8.18 ± 0.25). Moreover, the post-induction unpleasantness ratings (5.29 ± 0.22) were significantly lower compared to the unpleasantness ratings post-session (6.15 ± 0.24, $p = .018$). No other post hoc tests were significant. Furthermore, all three analyses showed effort level x time interactions (effort: $F(10,880) = 13.23$, $p^{GG} < .001$, $\hat{\eta}_G^2 = .20$; physical demand: $F(10,880) = 13.47$, $p^{GG} < .001$, $\hat{\eta}_G^2 = .03$; unpleasantness: $F(10,880) = 5.66$, $p^{GG} < .001$, $\hat{\eta}_G^2 = .01$; right panels in Figure 23), whereby generally, the rating differences between the five effort levels increased with

increasing time, independent of group. In addition, analysis of the effort ratings showed a group x time interaction, demonstrating that the control group had significantly higher effort ratings than the placebo group pre-induction (control group: 11.43 ± 0.34; placebo group: 9.82 ± 0.36; p = .024), while this was neither the case post-induction (control group: 9.92 ± 0.36; placebo group: 8.74 ± 0.39; p = .201) nor post-session (control group: 9.60 ± 0.38; placebo group: 9.35 ± 0.39; p = .996), independent of effort level.

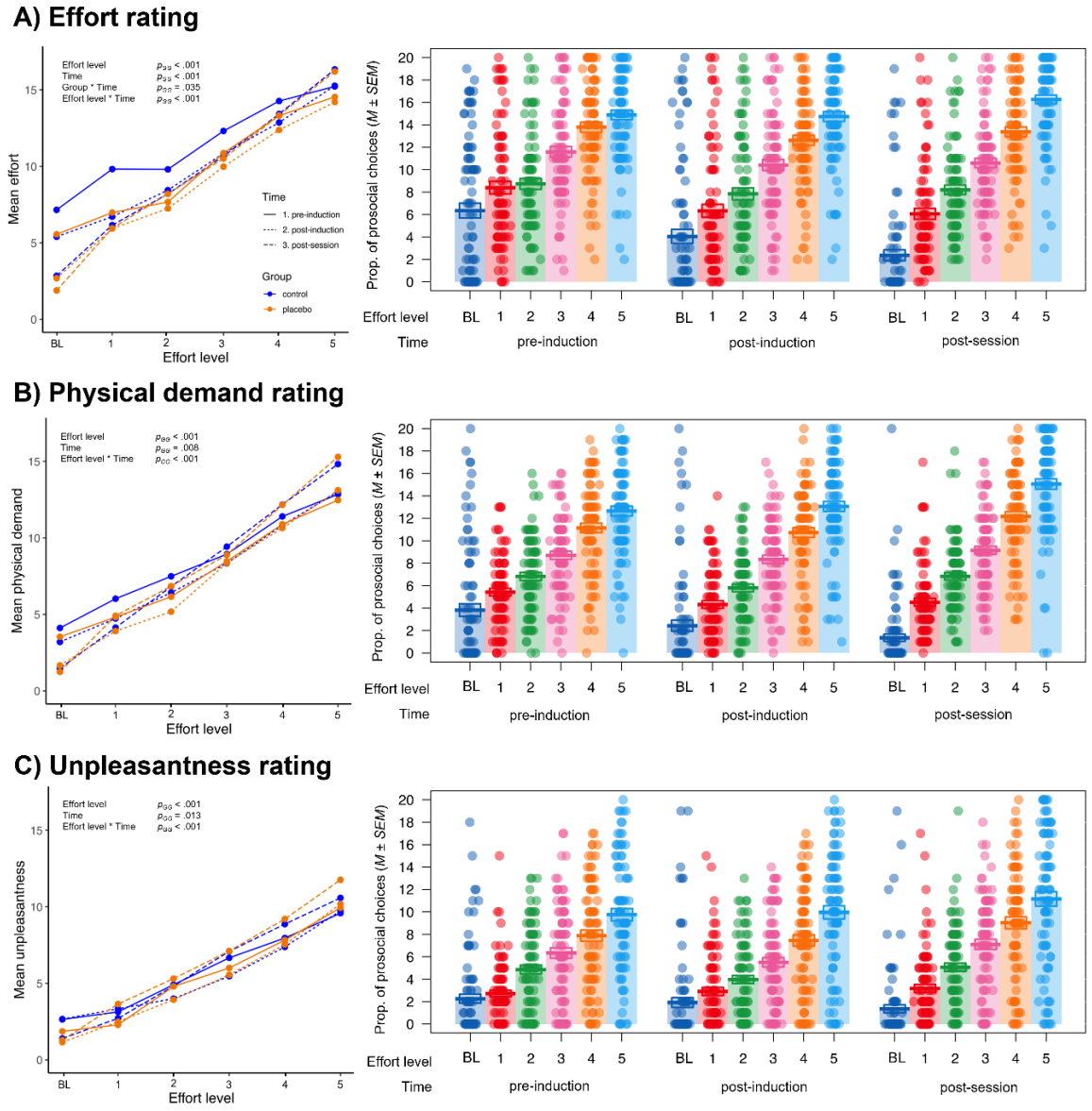

Figure 23. Manipulation check 1 evaluating the NASA Ratings regarding A) effort, B) physical demand and C) unpleasantness, including significant effects. Participants experienced and then rated each of the five effort levels (30, 40, 50, 60 and 70% of each participant's maximum voluntary contraction) they also received later in the task at three time points during the session: before the placebo induction (pre-induction), after the placebo conditioning (post-induction) and post-session. GG = Greenhouse-Geisser correction; BL = baseline rest (no effort exertion). Figure taken from Hartmann et al. (2022).

Importantly, we did not observe any other significant effects involving the factor group, showing that the three perceptions of the baseline and the five different effort levels were generally similar for the placebo and control group with this one exception.

Table 33

ANOVA of NASA effort ratings.

Effect	$\hat{\eta}^2_G$	90% CI	F	df	df_{res}	p
Group	.012	[.000, .075]	1.84	1	88	.179
Effort level	.396	[.337, .445]	311.53	5	440	< .001^{GG}
Time	.015	[.000, .051]	15.25	2	176	< .001^{GG}
Group × Effort level	.002	[.000, .000]	0.98	5	440	.389^{GG}
Group × Time	.004	[.000, .022]	3.65	2	176	.035^{GG}
Effort level × Time	.022	[.001, .029]	13.23	10	880	< .001^{GG}
Group × Effort level × Time	.002	[.000, .000]	1.39	10	880	.232^{GG}

Note. p values of effects including the factors effort level and/or time are reported using Greenhouse-Geisser (^{GG}) correction due to the violated assumption of sphericity.

Table 34

ANOVA of NASA physical demand ratings.

Effect	$\hat{\eta}^2_G$	90% CI	F	df	df_{res}	p
Group	.003	[.000, .049]	0.59	1	88	.446
Effort level	.496	[.443, .540]	384.74	5	440	< .001^{GG}
Time	.007	[.000, .034]	5.15	2	176	.008^{GG}
Group × Effort level	.002	[.000, .000]	0.66	5	440	.533^{GG}
Group × Time	.002	[.000, .016]	1.58	2	176	.209^{GG}
Effort level × Time	.027	[.004, .036]	13.47	10	880	< .001^{GG}
Group × Effort level × Time	.002	[.000, .000]	1.20	10	880	.309^{GG}

Note. p values of effects including the factors effort level and/or time are reported using Greenhouse-Geisser (^{GG}) correction due to the violated assumption of sphericity.

Table 35

ANOVA of NASA unpleasantness ratings.

Effect	$\hat{\eta}^2_G$	90% CI	F	df	df_{res}	p
Group	.000	[.000, .001]	0.01	1	88	.929
Effort level	.317	[.256, .367]	183.21	5	440	< .001^{GG}
Time	.007	[.000, .032]	4.81	2	176	.013^{GG}
Group × Effort level	.003	[.000, .000]	1.05	5	440	.349^{GG}
Group × Time	.002	[.000, .014]	1.37	2	176	.257^{GG}
Effort level × Time	.008	[.000, .008]	5.66	10	880	< .001^{GG}
Group × Effort level × Time	.001	[.000, .000]	0.84	10	880	.543^{GG}

Note. p values of effects including the factors effort level and/or time are reported using Greenhouse-Geisser (^{GG}) correction due to the violated assumption of sphericity.

Cover story. In the analyses of the three questions about the cover story (manipulation check 2), we observed no group differences regarding participant's perception of their anonymity in relation to the other participant ($t(72.51) = 0.81$, $p = .423$, 95% confidence interval (CI) [-0.10, 0.23], Cohen's $d = 0.17$; placebo group: $M \pm SEM = 4.84 \pm 0.07$, control group: 4.91 ± 0.04), their decisions being kept secret from the other participant ($t(87.85) = 0.36$, $p = .717$, 95% CI [-0.40, 0.57], Cohen's $d = 0.08$; placebo group: 4.31 ± 0.18, control group: 4.40 ± 0.17), and feelings of their decisions being monitored ($t(87.23) = 0$, $p > .999$, 95% CI [-0.55, 0.55], Cohen's $d = 0.00$; placebo group: 2.31 ± 0.20, control group: 2.31 ± 0.18). Generally, participants indicated high levels of kept anonymity and secrecy of their decisions. Participants of both groups expressed that they felt that their decisions were sometimes generally monitored.

Strength, motivation, and mood. Below we report the full results of the ANOVAs analyzing the maximum voluntary contraction (Table 36) as well as changes in positive (Table 37) and negative (Table 38) mood measured at three time points during the experimental session. Figure 24 shows the analysis of the three MVCs.

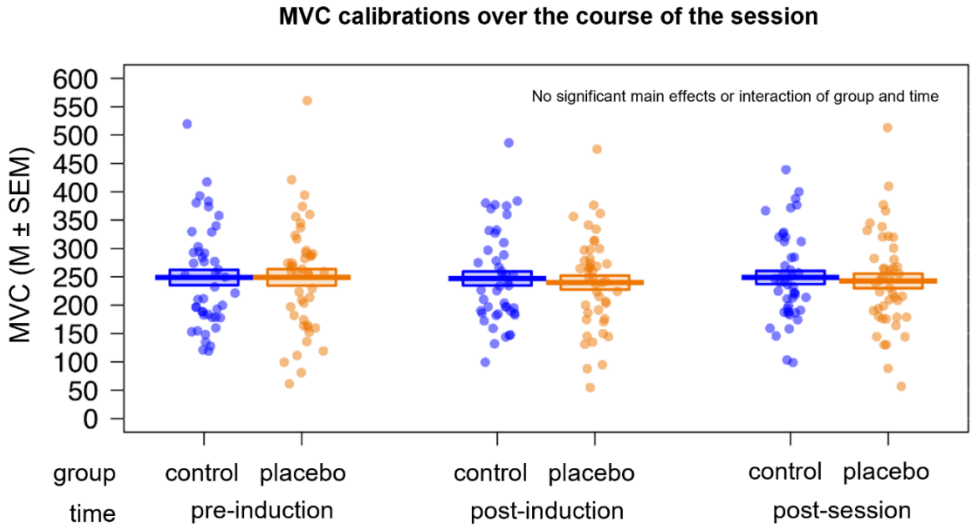

Figure 24. Post hoc analyses of maximum voluntary contraction (MVC) over the course of the session (each value was calculated as the average of two consecutive trials). We measured MVCs before (pre-induction) and after the placebo induction (post-induction) as well as at the end of the session (post-session) and compared them between the control and placebo group. Figure taken from Hartmann et al. (2022).

Table 36

ANOVA of maximum voluntary contractions over the course of the session.

Effect	$\hat{\eta}_G^2$	90% CI	F	df	df_{res}	p
Group	.001	[.000, .030]	0.06	1	88	.800
Time	.001	[.000, .002]	0.58	2	176	.561
Group × Time	.000	[.000, .000]	0.31	2	176	.736

Figure 25 shows the group comparison of the MVC (A), and force exerted (B) in the self-trial. Three subjects did not complete this task properly and thus had very low values, but exclusion of these subjects did not change the results.

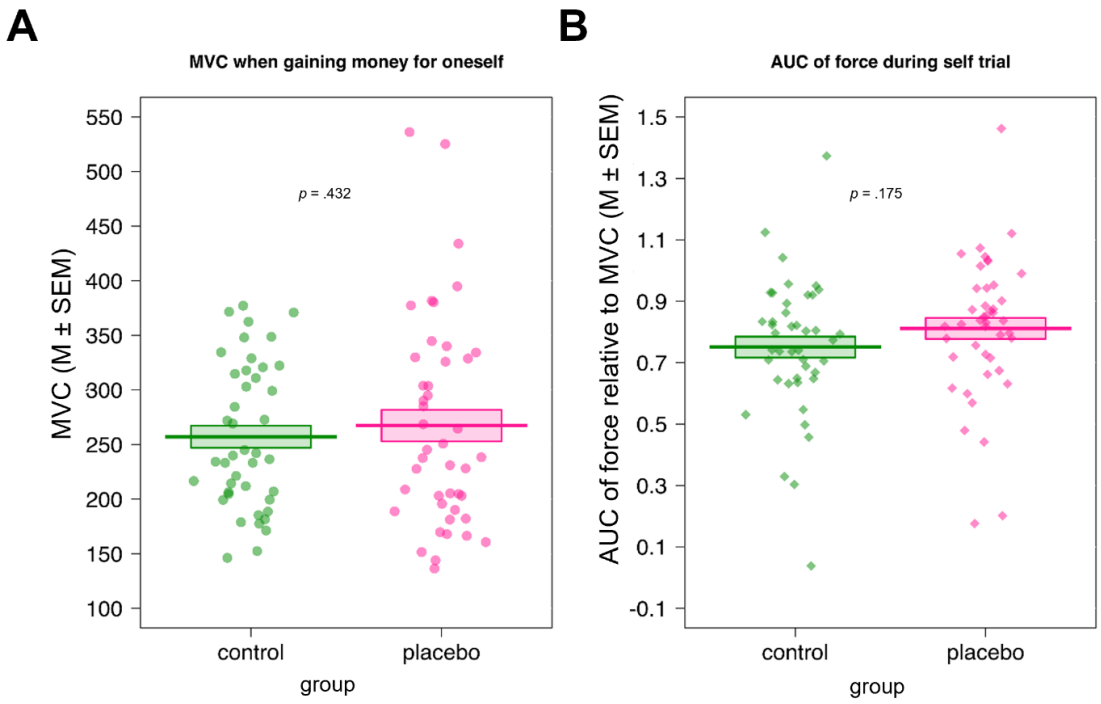

Figure 25. Preregistered analysis of the one-shot self-trial at the end of the prosocial effort task, where participants were told they could gain additional bonus money for themselves by pressing the grip force device as strongly as possible. This was operationalized once A) as the maximum voluntary contraction (MVC) and B) as the area under the curve (AUC) of the exerted force during that trial (B) and compared between the control and placebo group. Both measures showed no significant group differences, even when the three subjects, who did not complete the task properly, were excluded from the analyses. Figure taken from Hartmann et al. (2022).

Figure 26 shows positive and negative mood changes over the course of the session. Regarding participants' positive mood, we observed a main effect of time ($F(2,176) = 43.94$, $p^{GG} < .001$, $\hat{\eta}_G^2 = .09$), showing that positive mood was lower post-session (2.56 ± 0.07) compared to pre-induction (3.01 ± 0.06, $p > .001$) and post-induction (2.82 ± 0.07, $p = .010$), independent of group. Evaluating the participants' negative mood, we also observed a main

effect of time ($F(2,176) = 1.29$, $p^{GG} < .001$, $\hat{\eta}^2_G = .04$), showing that negative mood was lower post-session (1.17 ± 0.03) compared to pre-induction (1.30 ± 0.03, $p = .005$), again independent of group. However, negative mood was quite low in general (1.22 ± 0.02 on a scale from 1 to 5).

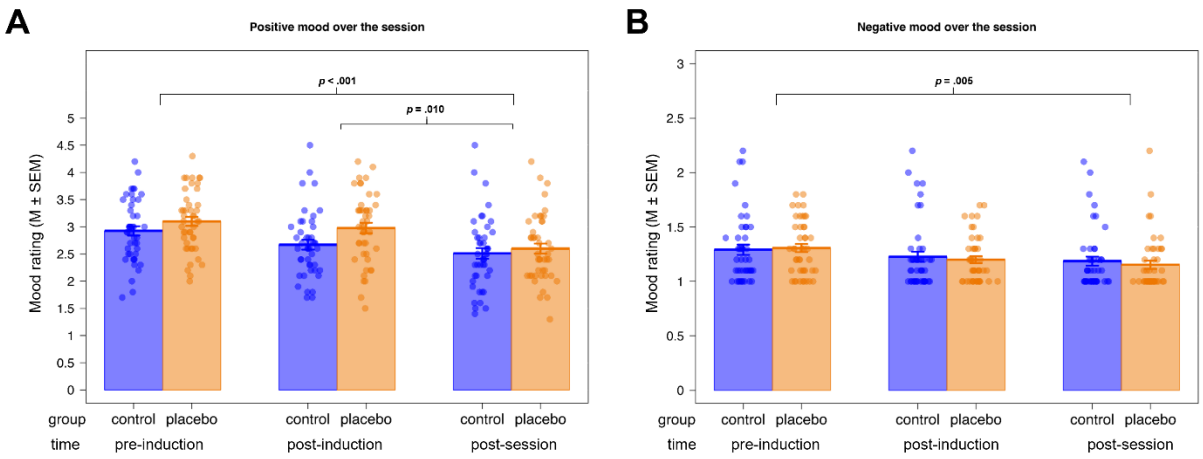

Figure 26. Post hoc analyses of A) positive and B) negative mood over the course of the session, as measured with the Positive and Negative Affect Schedule by Krohne et al. (1996). We observed main effects of time, whereby both positive and negative mood decreased over the course of the session. Figure taken from Hartmann et al. (2022).

Table 37

ANOVA of positive mood over the course of the session.

Effect	$\hat{\eta}^2_G$	90% CI	F	df	df_{res}	p
Group	.024	[.000, .100]	2.69	1	88	.104
Time	.088	[.029, .156]	43.94	2	176	$< .001^{GG}$
Group × Time	.005	[.000, .012]	2.50	2	176	$.089^{GG}$

Note. p values of effects including the factors effort level and/or time are reported using Greenhous Geisser (^{GG}) correction due to the violated assumption of sphericity.

Table 38

ANOVA of negative mood over the course of the session.

Effect	$\hat{\eta}^2_G$	90% CI	F	df	df_{res}	p
Group	.001	[.000, .032]	0.09	1	88	.764
Time	.038	[.002, .089]	12.92	2	176	$< .001^{GG}$
Group × Time	.002	[.000, .012]	0.53	2	176	$.558^{GG}$

Note. p values of effects including the factors effort level and/or time are reported using Greenhouse-Geisser (^{GG}) correction due to the violated assumption of sphericity.

Pre-effort empathy for pain. In the pre-effort empathy for pain task ANOVAs with either pain (Table 39) or unpleasantness (Table 40) ratings as outcomes, we only observed main effects of intensity, whereby painful stimulations the other person received were rated as

more painful/unpleasant than non-painful stimulations, independent of group. No other main effects or interactions were significant in either analysis.

Table 39

ANOVA of pain ratings in the pre-effort empathy for pain task.

Effect	$\hat{\eta}_G^2$	90% CI	F	df	df_{res}	p
Group	.002	[.000, .044]	0.34	1	88	.560
Intensity	.739	[.665, .792]	671.78	1	88	< .001
Group × Intensity	.002	[.000, .040]	0.36	1	88	.549

Table 40

ANOVA of unpleasantness ratings in the pre-effort empathy for pain task.

Effect	$\hat{\eta}_G^2$	90% CI	F	df	df_{res}	p
Group	.000	[.000, .026]	0.06	1	88	.814
Intensity	.409	[.282, .516]	230.60	1	88	< .001
Group × Intensity	.002	[.000, .040]	0.52	1	88	.472

Post-effort first-hand and empathy for pain task. In the post-effort first-hand and empathy for pain task ANOVA using the pain ratings as outcomes (Table 41), we observed a main effect of group ($F(1,88) = 7.34$, $p = .008$, $\hat{\eta}_G^2 = .81$), whereby the placebo group gave lower general ratings (3.52 ± 2.40) compared to the control group (3.93 ± 2.45), independent of intensity or target. We further observed a main effect of intensity ($F(1,88) = 1{,}852.53$, $p < .001$, $\hat{\eta}_G^2 = .04$), showing that, in general, painful stimulations (5.89 ± 0.09) were rated as more painful than non-painful stimulations (1.56 ± 0.07), independent of group or target. We also observed a main effect of target ($F(1,88) = 13.94$, $p < .001$, $\hat{\eta}_G^2 = .04$), showing that other-related stimulations (3.92 ± 0.17) were rated significantly higher than self-related stimulations (3.52 ± 0.19), independent of intensity or group. Furthermore, we observed a group x target interaction ($F(1,88) = 4.62$, $p = .034$, $\hat{\eta}_G^2 = .01$) showing that the difference between self- and other-related stimulation was bigger for the placebo (0.64 ± 0.19) compared to the control group (0.17 ± 0.11), independent of intensity. The significant intensity x target interaction ($F(1,88) = 10.58$, $p = .002$, $\hat{\eta}_G^2 = .01$) showed that the difference between painful and non-painful stimulation was higher for self- (4.57 ± 0.14) compared to

other-related stimulation (4.08 ± 0.12), independent of group. Finally, we observed a significant 3-way interaction between group, intensity, and target ($F(1,88) = 5.61$, $p = .020$, $\hat{\eta}^2_G = .01$), showing that the difference in the index (pain – no pain stimulation) between self- and other-related stimulation was bigger for the control (-0.85 ± 0.18) compared to the placebo group (-0.13 ± 0.24). This task was always done after the prosocial effort task.

Table 41
ANOVA of pain ratings in the first-hand and empathy for pain task.

Effect	$\hat{\eta}^2_G$	90% CI	F	df	df_{res}	p
Group	.036	[.000, .121]	7.34	1	88	.008
Intensity	.809	[.753, .848]	1,852.53	1	88	< .001
Target	.036	[.000, .120]	13.94	1	88	< .001
Group × Intensity	.005	[.000, .058]	2.36	1	88	.128
Group × Target	.012	[.000, .076]	4.62	1	88	.034
Intensity × Target	.013	[.000, .079]	10.58	1	88	.002
Group × Intensity × Target	.007	[.000, .063]	5.61	1	88	.020

In the second ANOVA using the unpleasantness ratings (Table 42), we only observed a significant main effect of intensity ($F(1,88) = 260.55$, $p < .001$, $\hat{\eta}^2_G = .40$), showing that, in general, painful stimulations (4.12 ± 0.21) the other person received were rated as more unpleasant than non-painful stimulations (1.38 ± 0.13), independent of group.

Table 42
ANOVA of unpleasantness ratings in the first-hand and empathy for pain task.

Effect	$\hat{\eta}^2_G$	90% CI	F	df	df_{res}	p
Group	.009	[.000, .069]	1.08	1	88	.302
Intensity	.401	[.273, .509]	260.55	1	88	< .001
Group × Intensity	.001	[.000, .024]	0.21	1	88	.648

Prosocial effort task. In the prosocial effort task, participants had an $M \pm SEM$ of 0.19 ± 0.05 (12/90 subjects, range = 0-2.67) % fail trials where they did not make a decision, and 1.30 ± 0.20 (43/90 subjects, range = 0-8.00) % fail trials where they did not manage to exert the chosen effort (both relative to all trials). These fail trials did not differ significantly between the groups (decision: $t(67.27) = -1.95$, $p = .055$, 95% confidence interval (CI) [0.09, 0.30]; squeezing: $t(85.03) = -1.20$, $p = .235$, 95% confidence interval (CI) [1.07, 1.54]).

Below we report the full results of the three main analyses of the prosocial effort task data (Tables 43 and 44: ANOVA and LMM with proportion of work offers chosen; Tables 45 and 46: ANOVA and LMM with reaction time (RT) when making the choice; Table 47: LMM of the area under the curve of the exerted force).

Table 43

ANOVA of the proportion of work offers chosen from the prosocial effort task.

Effect	$\hat{\eta}_G^2$	90% CI	F	df	df_{res}	p
Group	.010	[.000, .070]	1.96	1	88	.165[GG]
Effort level	.134	[.077, .183]	60.06	4	352	< .001[GG]
Shock reduction	.087	[.039, .130]	63.12	4	352	< .001[GG]
Group × Effort level	.001	[.000, .000]	0.35	4	352	.663[GG]
Group × Shock reduction	.006	[.000, .014]	4.10	4	352	.020[GG]
Effort level × Shock reduction	.030	[.008, .035]	13.11	16	1,408	< .001[GG]
Group × Effort level × Shock reduction	.003	[.000, .000]	1.20	16	1,408	.304[GG]

Note. Subject ID, group, effort level and shock reduction were entered into the ANOVA as factors; [GG] = Greenhouse Geisser sphericity correction.

Table 44

Analysis of Deviance (Type II Wald test) on a generalized LMM of the proportion of work offers chosen in the prosocial effort task.

Effect	χ^2	df	p
Group	1.97	1	.160
Effort level	562.14	4	< .001
Shock reduction	423.94	4	< .001
Group × Effort level	7.61	4	.107
Group × Shock reduction	13.89	4	.007
Effort level × Shock reduction	22.96	16	.115
Group × Effort level × Shock reduction	26.71	16	.045

Note. With choice as a binary outcome variable, we entered the factors group, effort level and shock reduction into a generalized LMM as fixed effects and included a subject-level random intercept. LMM = linear mixed model; AUC = area under the curve.

In the ANOVA analyzing the RTs (Table 45) when making a choice, we observed main effects of effort level ($F(3,352) = 69.84$, $p < .001^{GG}$, $\hat{\eta}_G^2 = .09$) showing that participants made their choices faster for lower effort levels, independent of group or shock reduction for the other (values in ms, effort level 1: 1082.40 ± 17.03; effort level 2: 1097.29 ± 18.13; effort level 3: 1194.24 ± 20.47; effort level 4: 1326.61 ± 24.11; effort level 5: 1446.51 ± 26.24). We further observed a main effect of shock reduction ($F(4,352) = 40.20$, $p < .001^{GG}$, $\hat{\eta}_G^2 = .03$),

showing that participants made their choice faster the more shocks they could prevent for the other person, independent of the effort level or group (values in ms, preventing 5 shocks: 1142.20 ± 19.31; 4 shocks: 1170.39 ± 20.87; 3 shocks: 1199.12 ± 21.77; 2 shocks: 1269.87 ± 24.25; 1 shock: 1347.48 ± 24.56). Lastly, we observed an effort level x shock reduction interaction ($F(16,1408) = 4.88$, $p < .001^{GG}$, $\hat{\eta}^2_G = .01$).

Table 45

ANOVA of the reaction time when making choices in the prosocial effort task.

Effect	$\hat{\eta}^2_G$	90% CI	F	df	df_{res}	p
Group	.015	[.000, .083]	2.15	1	88	$.146^{GG}$
Effort level	.094	[.045, .138]	69.84	4	352	$< .001^{GG}$
Shock reduction	.027	[.000, .052]	40.20	4	352	$< .001^{GG}$
Group × Effort level	.001	[.000, .000]	0.95	4	352	$.393^{GG}$
Group × Shock reduction	.001	[.000, .000]	1.24	4	352	$.346^{GG}$
Effort level × Shock reduction	.009	[.000, .006]	4.88	16	1,408	$< .001^{GG}$
Group × Effort level × Shock reduction	.001	[.000, .000]	0.60	16	1,408	$.829^{GG}$

Note. Subject ID, group, effort level and shock reduction were entered into the ANOVA as factors; ^{GG} = Greenhouse Geisser sphericity correction.

Table 46

Analysis of Deviance (Type II Wald test) on a LMM of the reaction time when making choices in the prosocial effort task.

Effect	χ^2	df	p
Group	4.01	1	.045
Effort level	97.67	1	< .001
Shock reduction	67.50	1	< .001
Group × Effort level	0.85	1	.356
Group × Shock reduction	0.15	1	.697
Effort level × Shock reduction	2.14	1	.144
Group × Effort level × Shock reduction	1.69	1	.193

Note. With reaction time as an outcome variable, we entered the factors group, effort level, and shock reduction as well as their interaction into a LMM as fixed effects. We also included a subject-level random intercept and random slopes for effort and shock reduction as well as their interaction. LMM = linear mixed model; AUC = area under the curve.

Table 47

Analysis of Deviance (Type II Wald test) on a LMM of the AUC of the force exerted in the prosocial effort task.

Effect	χ^2	df	p
Group	3.99	1	.046
Effort level	29424.90	4	< .001
Shock reduction	9.99	4	.040
Group × Effort level	3.05	4	.549
Group × Shock reduction	2.15	4	.708
Effort level × Shock reduction	140.12	16	< .001
Group × Effort level × Shock reduction	8.56	16	.930

Note. With force as an outcome variable, we entered the factors group, effort level and shock reduction into a LMM as fixed effects and included a subject-level random intercept. LMM = linear mixed model; AUC = area under the curve.

Correlations. Figure 27 shows the associations between the proportion of work offers chosen in the prosocial effort task and A) unpleasantness ratings, B) empathy for pain ratings, C) choice reaction time, and D) social value orientation.

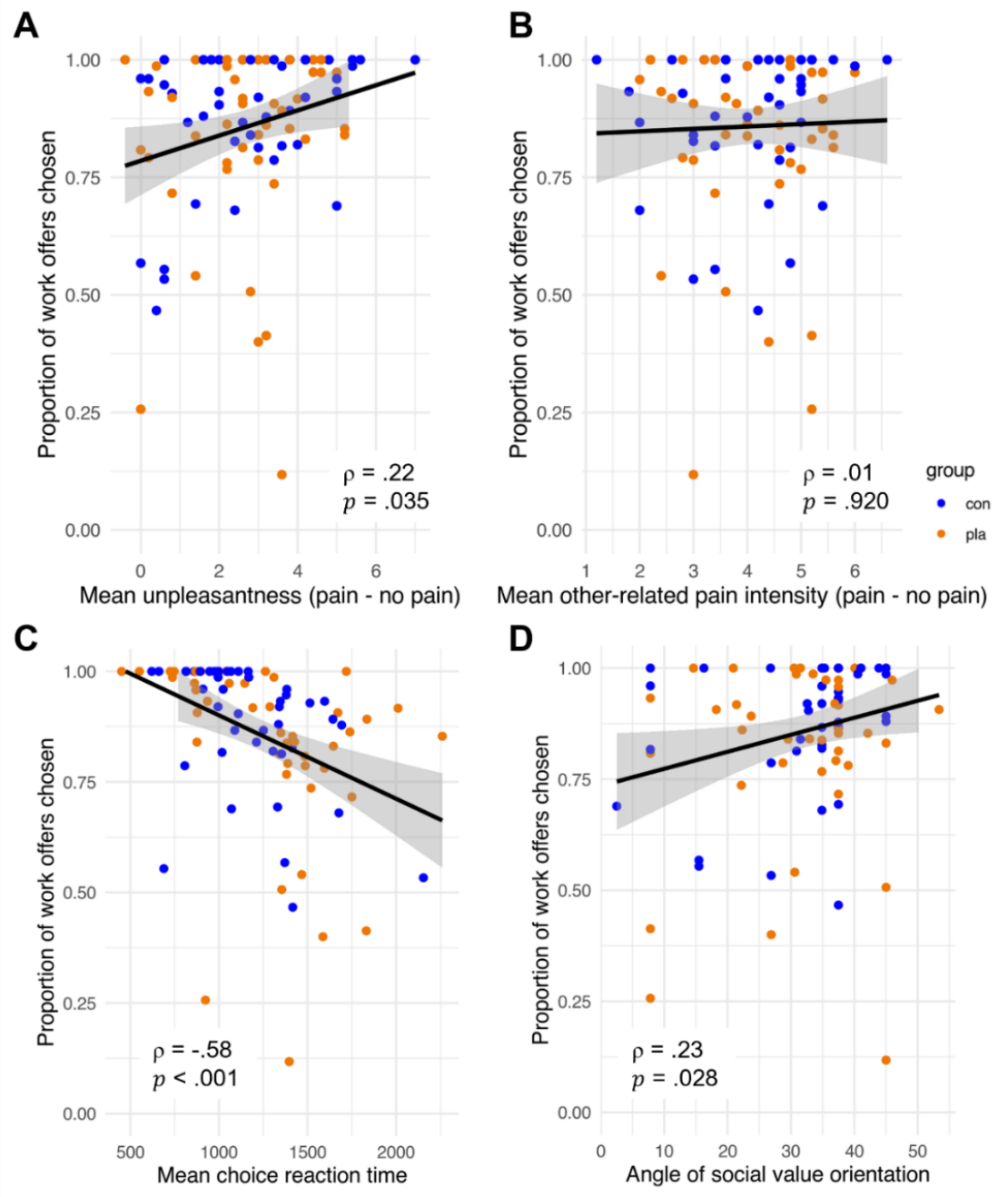

Figure 27. We computed Spearman correlations between the proportion of work offers chosen in the prosocial effort task and found A) a positive correlation with unpleasantness ratings, B) no correlation with empathy for pain ratings, C) a negative correlation with choice reaction time, and D) a positive correlation with social value orientation. All correlations were calculated over the whole sample, but color indicates group membership for display purposes: orange = control group (con); blue = placebo group (pla). We calculated correlations over the whole sample. Increased prosocial behavior in the choice task was associated to increased unpleasantness when observing others' pain, faster reaction times when making choices and higher other-related social value orientation. Figure taken from Hartmann et al. (2022).

5 General Discussion

"(...) to look beyond your own pain,
to see the pain of others."
– Yasmin Mogahed –

Since the seminal study of Singer et al. (2004) reporting for the first time an overlap in brain activation for first hand and empathy for pain and thus first hints for shared affective representations, crucial advances in psychology and social neuroscience have elucidated what mechanisms underlie empathy and prosociality. The present thesis, encompassing three preregistered, laboratory-based empirical studies, aimed to shed more light on the psychological and neural underpinnings of empathy and prosocial behavior in the domain of pain. Its goals were to 1) evaluate the existence of shared somatosensory representations between first-hand and empathy for pain and 2) gauge the connection between shared affective representations and prosocial behavior. Its findings contribute to our knowledge regarding the causal role of our own, somatic pain processing for the perception of and reaction to pain in others. In the following general discussion, the studies will be discussed in relation to each other and considering the current literature. A short summary of the main results and conclusions of each study will be followed by highlighting overarching strengths, specifically regarding the employed research methods. The thesis closes with an outline of limitations leading to future research directions and a final conclusion.

5.1 Summary of all studies

All three studies employed placebo analgesia, a causal-experimental manipulation to directly down-regulate first-hand pain, and then gauged its effects on empathy for pain or prosocial behavior using specifically tailored experimental designs and tasks. The first research objective of this thesis was to quantify the specific contribution of one's own somatosensory pain experiences to pain empathy: Chapter 3 includes two empirical studies

that investigated whether shared representations for first-hand and empathy for pain extend beyond the affective-motivational to the sensory-discriminative component of pain.

Study 1 in Chapter 3.2, titled "Another's pain in my brain: No evidence that placebo analgesia affects the sensory-discriminative component in empathy for pain" employed a cue-based first-hand and empathy for pain task where participants either received electrical stimulation themselves on the right or left hand in different intensities, or empathized with another participant receiving such stimulation. Before completing this task, first-hand pain sensitivity of the participants had been downregulated specifically on the right hand via a localized placebo analgesia induction. We hypothesized that placebo analgesia would reduce participants' first-hand and empathic pain perception only in the right hand, where placebo analgesia was induced, which would speak for the existence of shared representations on the somatosensory level. Behavior and brain activation in relation to the right hand was compared to each participants' left hand, which served as a control condition of unaltered pain sensitivity. As expected, placebo analgesia successfully downregulated first-hand pain in the right but not the left hand. We also replicated the previously reported activation overlap between first-hand and empathy for pain in affective-motivational brain regions. However, we found no evidence for an empathy modulation in our behavioral or neuroimaging data, which does not support the existence of shared somatosensory representations in empathy for pain.

Previously, somatosensory activation during empathic processing was most often found using picture-based tasks that show explicit visual depictions of others' pain (in comparison to the cue-based task of Study 1 which used abstract cues signaling electrical stimulation in different intensities). To rule out that the observed absence of evidence for somatosensory sharing in Study 1 was due to the type of task, Study 2 in Chapter 3.3, titled "Placebo analgesia does not reduce empathy for naturalistic depictions of others' pain in a

somatosensory specific way" corroborated the null findings of Study 1 in the same sample using a picture-based empathy for pain task. Participants observed and rated either the left or right hand in pictures of other individuals in everyday painful situations, after the same localized placebo analgesia manipulation on their own right hand. Again, we found no evidence for a somatosensory specific modulation of empathy for pain as a result of placebo analgesia. In exploratory analyses, we observed increased AI activity for right (compared to left) hands in painful situations. This increased activity was thus observed in relation to the condition corresponding to one's own hand, where placebo analgesia had been induced.

These two studies did not provide supportive evidence for somatosensory shared representations in two classically used empathy for pain paradigms, a cue-based and a picture-based task. This suggests that sharing the pain of others might also be possible with blunted first-hand pain experiences focused on a specific body part and still engage shared neural networks limited to brain regions coding for affective-motivational aspects (AI and aMCC). The findings further show that, no matter how we infer the pain of another person (by imagining it with the help of cues or seeing it directly in pictures) and where the participants' attention is directed to, somatosensory brain regions (S1 and S2) seem to be less involved when sharing and representing others' pain, compared to previously reported affective regions. Instead, individuals might focus more on the general aspects of others' painful experiences when empathizing (e.g., how unpleasant the pain is for the other person and/or how unpleasant it is for oneself to witness that pain), as opposed to specific localized aspects (e.g., the exact location, type or duration of the other's pain). In other words, the results of Studies 1 and 2 suggest that we share the affective consequences of another's painful situation ('I understand and share that my friend is in pain') rather than sharing others' pain representations specifically in relation to their precise bodily origins, i.e., the exact nociceptive source ('I empathize with the right hand that my colleague hurt' or 'I feel

the pain in my friend's left foot'). Taken together, the findings of Chapter 3 add valuable information about the specificity of shared representations regarding the sensory-discriminative component in pain empathy and inform existing models aiming to explain the processing of empathy in the brain.

The second research objective of this thesis was to investigate the contribution of one's own pain experiences and shared affective representations to prosocial behavior: Chapter 4 includes Study 3, titled "Placebo analgesia reduces costly prosocial helping to lower another's pain", which showed that reduced first-hand pain may extend beyond affecting our emotional resonance and is able to influence how we act towards others in pain. Downregulating participants' general pain sensitivity via a placebo pill, individuals under the influence of placebo analgesia behaved less prosocially compared to control participants with unaltered pain sensitivity. This was visible in less willingness to put in physical effort to prevent shocks for another person, slower reaction times when deciding whether to help or not, and less energy exertion even when having decided to put in said effort. And while we did not observe significant group differences in self-reported empathy for pain and unpleasantness as a result of the placebo manipulation, the degree of unpleasantness participants felt when witnessing the other person in pain was associated with a higher proportion of prosocial choices to reduce the pain of that person. The findings of Study 3 demonstrate that what we feel in our own body may shape what we do for other individuals, although this mechanism may not necessarily (only) happen via the route of sharing another's pain. Instead, other cognitive and motivational factors might regulate moral decision-making over a different route than the individual degree of empathy. For example, Lamm, Batson, et al. (2007) highlight that whether the observation of others' distress leads to a) empathic concern and increased altruistic motivation, or b) personal distress and egoistic motivation may critically depend on our individual abilities for self-other distinction and perspective-

taking: These cognitive abilities led to a change in neural activity in relation to others' pain in regions such as the insula and aMCC. In line with this, Lockwood et al. (2014) reported no association between trait-based empathy and prosocial behavior in people with high cognitive reappraisal, a cognitive strategy in which negative affect is decreased to focus on positive aspects of a situation. In contrast, this association was significant only for individuals with lower or average tendency to reappraise. The findings of Study 3 thus further specify and inform the shared representations account by adding the component of prosocial behavior, with the latter partly depending on how we feel our own and how we share others' painful experiences. They underline that there might be more than one single way to empathize with and help someone in pain.

5.2 Strengths

The three studies had important methodological strengths that will now be discussed in turn below, especially in light of their broader contributions to the conclusions of this thesis.

All studies successfully induced placebo analgesia, i.e., a down-regulation of first-hand pain sensitivity via a global (pill) or local (gel) manipulation. This induction procedure was a prerequisite to measure the effects of blunted first-hand pain sensitivity on empathy for pain and prosocial behavior, and allowed us to causally investigate the existence of shared representations. The success of this induction was visible on many levels. In the manipulation checks assessing the magnitude and duration of the placebo response, we found reduced subjective first-hand pain ratings and typical pain and placebo analgesia networks in the brain (see Geuter et al., 2017 for a review and Amanzio et al., 2013; Zunhammer et al., 2021 for meta-analyses). Analyses also showed no evidence for a significant decrease of placebo responses over the course of the experimental session, and thus a stable effect of placebo analgesia over time. It is important to note that, as part of the induction procedure, participants were told that the gel or pill they received would affect their own pain

processing, while it was made clear that the second participant never received any treatment and whose pain sensitivity thus remained unaltered. Any transfer effects to empathy for pain and prosocial behavior we observed because of the placebo analgesia manipulation were therefore not due to expectations regarding the changed pain perception of the other person. Together, this provided strong evidence for the validity of our employed method and corroborated any found transfer findings or the absence of such.

All studies used a dichotomous approach to classify responders and non-responders to the placebo analgesia inductions, based on previously used criteria. Non-responders were excluded from the main analyses, as the existence of a first-hand placebo response was necessary for the tested downstream effects on empathy and prosocial behavior. However, future research might benefit from assessing the placebo response as a continuum from high to low responding, and include more dimensional measures of analgetic responses, such as pre- vs. post-ratings of painful stimuli. Along the same lines, non-responders also represent a so-far understudied population that could act as an interesting comparison group to placebo responders (Frisaldi et al., 2018). For example, future work could focus on investigating more nuanced individual differences, i.e., whether people with stronger first-hand placebo responses also show the strongest decreases in empathy and prosocial behavior and thus increased sharing of their own somatosensory pain representations. This could help in understanding the complexity of shared representations and shed more light on individual differences.

As our predictions in Studies 1 and 2 were not confirmed, the planned analyses were supported by an additional Bayesian framework to report relative evidence for vs. against the null hypothesis (Keysers et al., 2020). By providing more direct evidence for the null hypothesis and publishing non-significant findings, this thesis therefore actively counteracts publication bias (whereby the nature of a result influences the probability of it being

published; Scheel et al., 2021) and the file drawer problem resulting from this bias. Moreover, all studies were preregistered on the Open Science Framework, with especially the study design as well as the confirmatory hypotheses and most of the analyses fixed prior to the start of the data collection (Crüwell, Stefan, et al., 2019). The practice of preregistering comes with great benefits: Increased transparency of objectives, hypotheses, design and analyses, clearly separating confirmatory from exploratory research and minimizing researchers' degrees of freedom (Simmons et al., 2011; Wicherts et al., 2016). It also avoids overconfidence in post hoc explanations and decreases the likelihood of believing that there is evidence for false positive results (Nosek et al., 2018). Wherever the preregistration did not specify certain decisions (e.g., the exact coordinates of the ROIs in Studies 1 and 2), this was clearly indicated when reporting and writing up the analyses and their results. Although all studies included some deviations from the preregistration in their final analyses due to omissions of study design or analysis details, minor errors in planning statistical analyses, as well as adding of post hoc exploratory analyses, these deviations are outlined transparently within each chapter, and the main results focus on the preregistered hypotheses and analyses. Adding to the strength of conducting preregistered, transparent and reproducible research, we used the CRediT system in all chapters to transparently document each author's specific contribution (Allen et al., 2019; Brand et al., 2015). We further provide the Citation Diversity Statement in Chapter 2.8 (Zurn et al., 2020) to raise awareness and help mitigate gender biases in citations (Dworkin et al., 2020), one of the many issues women face in academia (see Gruber et al., 2021 for a review). Moreover, each studies' sample sizes were pre-planned and optimized using either a priori power analyses or other justifications specified before the data collection, which further bolsters the interpretability of the reported results.

The published Studies 1 and 2 are available open-access (see Dai et al., 2018; Okune et al., 2020 for reviews) and all studies have freely available preprints of their respective submitted

versions published on public repositories such as BioArXiv (Fraser et al., 2020). All studies also generated output and resources next to the manuscripts themselves: Each task was designed to overcome shortcomings of previous research and represents an updated version of established measures of first-hand pain, empathy for pain or prosocial behavior: Study 1 used a new version of the cue-based empathy for pain task based on the one employed in Singer et al. (2004) and Rütgen, Seidel, Silani, et al. (2015), with template stimuli freely available online (https://osf.io/5y34e/). Study 2 built an updated stimuli set for the picture-based empathy for pain task used in Jackson et al. (2005). The stimuli were not directly uploaded to an online repository as they have only been used in two studies so far (one of those validating the comparability of painful and non-painful left- vs. right-hand stimuli) and are thus not independently validated by other researchers yet. Study 3 adapted and combined two previous decision-making tasks by Crockett et al. (2015) and Lockwood, Hamonet, et al. (2017) to use effort exertion for shock prevention as a measure of prosocial behavior. This task combines explicit with more implicit outcome measures (choice behavior, reaction times as well as the energization put into actions), which can be related to subjective ratings and trait measures. Such complementary insights are critical to study complex psychological phenomena such as empathy and prosocial behavior. Lastly, detailed documentation on the used methods available in the Supplementary Materials of the respective manuscripts allows for those resources to be freely used and the present results to be replicated by future studies.

5.3 Limitations and future directions

Despite these strengths, the studies also had some shortcomings that might have influenced the results and offer possible future research questions and directions.

Our findings did not provide causal evidence for somatosensory sharing, despite many past studies highlighting the role of somatosensory cortices for representing the pain of others (Keysers et al., 2010; Riečanský & Lamm, 2019 for reviews). Although we did not find

evidence for a causal involvement of the primary or secondary somatosensory cortex in perceiving others' pain, this does not exclude an involvement of these, or other somatosensory-related, regions in serving other purposes related to empathic processing. In our specific experimental situation, a fast and effective processing of the situation was possible that did not necessarily require specific somatosensory-related knowledge of the other's pain. However, there might be other situations in which the exact localized consequences of pain for another person increase in relevance: For example, medical professionals who treat people in emergency situations might process the pain of others in a more localized way, as they are in situations warranting more specific knowledge about the origin of that pain. Likewise, somatosensory representations might more relevant in situations where one's own health is in danger, and current first-hand pain processing more directly matches the observation of pain in others. This also fits with prior literature suggesting sensorimotor activations to another's pain reflecting "activation of defensive responses in agreement with the goal of pain" that serves to protect the body from external harm (Riečanský & Lamm, 2019, p. 970). Therefore, somatosensory sharing might happen only in specific situations that require concrete helping (Gallo et al., 2018) or knowledge of the pain source. This does not, however, fully explain the somatosensory activation observed in especially picture-based empathy for pain tasks, where the source of pain is shown but not needed to empathize with the other person in pain. Extending our here used causal approach of placebo analgesia to other causal methods such as TMS to study the exact contexts in which knowing the source of another's pain, and thus increased involvement of somatosensory regions, is necessary, is a promising future research direction.

We observed an increase in AI activity during viewing of right hands in pain which corresponded to one's own hand where placebo analgesia was induced. Wager et al. (2011) highlighted differential pain evaluation in individuals with strong placebo responses that do

not necessarily mean a complete blockade of noxious input. Furthermore, placebo-related increases in neural activity are quite common (e.g., in AI; Petrovic et al., 2002, 2005; Bingel et al., 2006), and should be studied further in the future, especially in what way placebo-related increases and decreases in brain activity contribute to our evaluation of and behavior to others' pain. This knowledge could be especially valuable in investigating shared representations, as it could show that sharing another's pain might be possible both through activation and downregulation of specific brain regions. In this regard, studies investigating empathy in the domain of pain have mainly contrasted affective and somatosensory regions belonging to the two main pain networks in the brain, the affective-motivational and the sensory-discriminative component. Future research may profit from extending efforts in elucidating the existence of shared representations to other regions involved in modulatory control of emotional responses, such as dorsolateral, medial, and orbitofrontal cortices as well as inferior frontal gyrus, or connect research on shared representations to regions responsible for processing reward, such as the striatum and nucleus accumbens. These efforts would also help in shedding more light on the role of more cognitive, top-down processes during empathy and prosocial behavior.

All studies in this thesis were conducted on neurotypical samples with no history of or current psychiatric or neurological conditions. Studying these processes broadly related to social cognition abilities in a homogeneous sample helps understand the basic mechanisms underpinning them, but it is also important to consider implications for conditions where these abilities are impaired and qualitatively different (Shackman & Wager, 2019). For example, the here presented findings are highly relevant for empathic processing in different pain conditions, such as chronic pain (Ma et al., 2020; Zhang et al., 2021) or congenital insensitivity to pain (CIP; Danziger et al., 2006, 2009). These groups represent two extremes on a dimensional scale from no to high daily pain that can be studied in addition to typical

pain perception in neurotypical samples to better understand how a qualitatively distinct first-hand pain processing affects empathy and prosocial behavior. For example, people with daily pain experiences in certain body parts, such as chronic low back pain, irritable bowel syndrome or migraine, might be able to share the same type of pain in other individuals more specifically by using their own somatosensory pain representations, or may be less empathic because of a constant excess of first-hand pain. People with CIP might put more weight on the affective representation of others' pain experiences, as this group of individuals never experienced direct, first-hand somatosensory pain experiences themselves (Danziger et al., 2009). Similarly, people who feel the pain of others consciously in their own bodies, vicarious pain responders (Bowling et al., 2019; Grice-Jackson et al., 2017ab) and mirror-sensory synesthetes (Ioumpa et al., 2019) both represent fascinating groups of individuals to study the effects of heightened empathic resonance. Do these groups use different ways to empathize with others, possibly engaging somatosensory brain regions to a stronger or lesser extent? More research on these diverse patient populations is needed to fully understand how a non-typical first-hand pain experience is related to empathy for pain and how that further affect prosocial motivation and behavior.

Psychiatric conditions such as depression, autism spectrum disorder, alexithymia, or psychopathy are all characterized by a different way to understand and/or resonate with others' emotions (Farrow & Woodruff, 2007; Lockwood, 2016; Zahn-Waxler & Schoen, 2016 for reviews). However, studying empathy and prosociality in such clinical samples warrants new study designs adapted to their unique characteristics, especially considering sample heterogeneity, comorbidities, feasibility, and ethical concerns. Nevertheless, future scientific efforts should be made to ultimately aid individuals with such conditions in better understanding their own and others' emotions as well as react accordingly, despite their respective impairments. Researching the basic mechanisms that lead to intact empathic

responses and behavior may then hopefully inform therapeutic interventions and trainings to modulate and improve sharing and regulation of others' emotions. In this regard, new models of 'adaptive empathy' have been proposed that consider not only the empathizer, but also the person being empathized with. In this promising framework, feedback and learning from others may flexibly change empathic responses depending on the context (Shamay-Tsoory & Hertz, 2022). In line with this, we observed a related situation-specific degree of helping in Study 3, where people under the influence of placebo analgesia varied their helping dependent on how much they can help in a given situation. Investigating the role of vicariously sharing someone else's emotions using new measures of adaptive empathy could be an exciting new research direction.

In the here presented studies, we excluded individuals actively taking psychopharmacological medication or experiencing pain-related conditions and nevertheless report effects of placebo analgesia (i.e., the belief of having taken a single-dose pain medication) on social motivation and behavior in multiple measures. This is in line with past research indicating medication intake affecting emotion perception, empathy and motivation, both in humans (Carlyle et al., 2019; Kroll et al., 2021 for opioid use; DeWall et al., 2010; Durso et al., 2015; Mischkowski et al., 2016, 2019; Roberts et al., 2019 for acetaminophen; Rütgen et al., 2019 for antidepressants) and animal models (Kandis et al., 2018 for acetaminophen; Nazeri-Rezaabad et al., 2020 for morphine). In light of the current opioid crisis (Vadivelu et al., 2018) and as typical medication use in the population may be much higher (Mehuys et al., 2019) than reflected by our study samples, including medication history into future studies as a covariate becomes especially important.

While inspired by previous findings and strongly oriented on past, similar studies, the here included studies contain important differences such as changes in study design and location, timing of the measured effects in relation to the placebo induction and framing of the cover

story and tasks. As already highlighted by previous studies (Lamm et al., 2011), the choice of task to measure empathy for pain can lead to very different results, especially on the neural level. For example, the empathy tasks used in the present thesis were either changed (Studies 1 and 2, where the task was adapted to investigate somatosensory sharing) or not the main focus of the experiment (Study 3, where the focus was on measuring prosocial behavior). These differences need to be taken into account when interpreting existing or planning future studies. Especially because of these study differences, we report standardized effect sizes wherever possible to encourage and facilitate comparisons between different studies (Lakens, 2013).

Moreover, the analyses of the fMRI data in Studies 1 and 2 purposefully did not disentangle anticipation from presentation phases of electrical or visual stimuli to keep comparability to previous studies (Rütgen, Seidel, Riečanský, et al., 2015; Rütgen, Seidel, Silani, et al., 2015). Furthermore, anticipation phases were much longer (7-11 seconds) compared to the stimulus delivery / picture presentation phase (0.5-3.5 seconds), which could have led to exaggerated anticipatory processing in the measured and modelled brain signatures. Since research has identified separate mechanisms for these two phases (Peng, Huang, et al., 2019; Peng, Peng, et al., 2019), this distinction should also be taken into account for the future assessment and quantification of pain empathy.

Furthermore, Studies 1 and 2 did not include a between-subjects control group who was not under the influence of placebo analgesia, which makes direct comparisons to previous between-subjects studies difficult (Rütgen, Seidel, Riečanský, et al., 2015; Rütgen, Seidel, Silani, et al., 2015) and limits conclusions regarding a general down-regulation of empathic reactions in behavior and affective brain regions by placebo analgesia. This also relates back to the differentiation between treatment/tonic vs. stimulus/phasic expectancies in response to a certain treatment: While the former expectancies consist of relatively stable prior

knowledge, memories and subjective beliefs, the latter adapt flexibly based on moment-by-moment updates and evaluation of prediction errors in regard to certain stimuli (Atlas et al., 2010). Our exploratory findings of a generalized placebo response through our localized placebo induction in Studies 1 and 2 could speak for an affect-modulating role of the opioid system and enhanced situational modifiability of somatosensory responses for first-hand pain compared to empathy for pain. Future research should aim to more specifically tease apart tonic vs. phasic influences and evaluate their importance in terms of how downregulating pain sensitivity via placebo analgesia localized to a certain body part influences general emotion perception and affect sharing (Benedetti & Amanzio, 2013; Nummenmaa & Tuominen, 2017 for reviews).

In this regard, although an upregulation of the opioid system through placebo analgesia was assumed based on previous studies (King et al., 2013; Rütgen, Seidel, Silani, et al., 2015; Rütgen et al., 2021), none of the studies presented here directly tested whether this was the case. This limits the conclusions the results have in terms of their underlying neurochemical mechanisms. Directly linking the effects of placebo analgesia to the opioidergic system or other neurotransmitter systems and gauge its effect on empathy for pain should be the focus of future research, building on the work of Rütgen and colleagues (Rütgen, Seidel, Silani, et al., 2015; Rütgen et al., 2018, 2021). These efforts could be realized by explicitly testing the involvement of opioidergic mechanisms in placebo analgesia using positron emission tomography, or by employing pharmacological manipulations of opioid agonists and antagonists, such as morphine or naltrexone, respectively. As pain modulation has been shown to engage not only the opioidergic system, but also other neurotransmitter system such as the dopaminergic or endocannabinoid systems (Frisaldi et al., 2020), future work should aim to study the complex interplay between different systems and their specific roles in contributing to empathic processing.

It has to be noted that the power analyses of Studies 1 and 2 were based on behavioral data of previous studies and not on brain data. Improved sample size calculation approaches such as the safeguard power analysis (Perugini et al., 2014) or fMRI data-specific power analyses (Mumford, 2012) might help in calculating the needed sample size to find a certain effect even more sensitively in the future (Lakens, 2022).

Empathy has primarily been studied in the domain of physical pain, as evident in this thesis, with some previous research also focusing on social pain (Carlyle et al., 2019; Wesselmann et al., 2009), gustation (Jabbi et al., 2007; Wicker et al., 2003) and touch (Bufalari & Ionta, 2013; Keysers et al., 2004; Lamm et al., 2015). However, empathy is not limited to pain or even to negative emotional states. For example, affective touch represents an interesting modality that can be induced both for negative and positive valences and can be compared to somatic pain, as both involve an external stimulus being applied to a body part (e.g. as in Rütgen et al., 2021). This study recently found that placebo analgesia also affected first-hand and empathic experiences of unpleasant touch, which implicates domain-general shared representations. On the other hand, administration of an opioid antagonist did not block these effects, supplying causal evidence for a pain-specific involvement of the opioid system in pain empathy. Current and future efforts should try to incorporate measuring affect sharing for others' positive experiences or directly relate empathy for positive and negative emotional states with each other to compare the underlying similar vs. distinct neural networks. This would shed more light on whether the here presented findings are specific to pain, specific to negative emotions, or generalize to other valences and modalities.

Lastly, the above-mentioned efforts demonstrate the importance and necessity of conducting open, reproducible, and transparent science, but also show that even preregistration has its shortcomings and cannot anticipate or fix all aspects of a scientific research project. This underlines the necessity of a shift in research culture where more time

is allocated to the planning phase before the data collection, to refine hypotheses, design, and analyses, using feedback directly from peers in the research community. In this regard, Registered Reports, which are increasingly employed to counteract both publication bias and the file drawer problem (Chambers & Tzavella, 2021; Crüwell, Stefan et al., 2019; Scheel et al., 2021), stand as an additional future step beyond the here presented efforts.

5.4 Final conclusion

This dissertation refined the specificity and apparent limits of using our own pain representations to share the suffering of others in our social environment. The here presented findings suggest that shared representations between first-hand and empathy for pain indeed exist but might be situated on a different level than previously suggested, highlighting the importance of task choice and design specifics for results interpretation. Specifically, they clarify the unique way in which our own pain processing contributes to our emotions, motivation, and behavior, hinting that there might be many ways to empathize with and subsequently choose to help someone in pain. Possibly using different brain networks to represent different pain states in different situations, our empathic responses may strongly depend on the context and relevance of the observed pain for ourselves or for others. Showing how a down-regulation of one's own pain sensitivity may transfer to our perception and actions regarding the others' painful experiences demonstrates how pivotal an intact pain processing system is for understanding others' pain. Elucidating the specific psychological and neurophysiological mechanisms that underlie empathy and prosocial behavior may ultimately enhance the understanding of clinical conditions with aberrant pain processing and its implications for social cognition. For us as individuals, such insights may pave the way to better regulate and react to the multitude of suffering observed in our society – may this be empathizing with a colleague who accidentally hit their elbow, a friend who recently lost their job or a homeless person on the street asking for money.

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7 Annex

7.1 List of Tables

7.2 List of Figures

7.3 Abbreviations

ACC	Anterior cingulate cortex
AI	Anterior insula
aMCC	Anterior midcingulate cortex
AMI	Apathy Motivation Index
ANOVA	Analysis of variance
AQ-k	Autism Quotient, short version
BDI-II	Beck Depression Inventory, 2nd version
BF_{10}	Bayes Factor comparing evidence for the alternative vs. null hypothesis
BF_{01}	Bayes Factor comparing evidence for the null vs. alternative hypothesis
BOLD	Blood oxygen level dependent
CIP	Congenital insensitivity to pain
CRediT	Contributor Roles Taxonomy
CSF	Cerebrospinal fluid
CTR	Control
dlPFC	Dorsolateral prefrontal cortex
EHI	Edinburgh Handedness Inventory
ERP	Event-related potential
FIR	Finite impulse response
fMRI	Functional magnetic resonance imaging
FWE	Family-wise error
FWF	Fonds zur Förderung der wissenschaftlichen Forschung [Austrian Science Fund]
FWHM	Full-width at half-maximum
(G)LMM	(Generalized) Linear Mixed Model
H_0	Null hypothesis
H_1	Alternative hypothesis
HARKing	Hypothesizing after the results are known
HAS	Helping Attitudes Scale
IRI	Interpersonal Reactivity Index
K	Discount parameter
LIDAS	Lifetime Depression Assessment Self-report
LPI	Lateral Preference Inventory
LQ	Laterality quotient
mA	Milliampere
M	Mean
MAIA	Multidimensional Assessment of Interoceptive Awareness
MANOVA	Multivariate analysis of variance
MOR	μ-opioid receptor
MVC	Maximum voluntary contraction
NPS	Neurological pain signature
OSF	Open Science Framework

p	preregistered
PANAS	Positive and Negative Affect Schedule
PLA	Placebo
QCAE	Questionnaire of Cognitive and Affective Empathy
REX	Response Exploration for Neuroimaging Datasets
ROI	Region of interest
S1/S2 or SI/SII	Primary/secondary somatosensory cortex
SCR	Skin conductance response
SD	Standard deviation
SD3	Short Dark Triad
SEM	Standard error of the mean
SPM12	Statistical Parametric Mapping Version 12
STAI	State-Trait Anxiety Inventory
SVC	Small volume correction
SVO	Social Value Orientation Scale
TAS-20	Toronto Alexithymia Scale, 20-item version
TE	Echo time
TR	Repetition time
VAS	Visual analogue scale
VDM	Voxel displacement map
VPQ	Vicarious Pain Questionnaire
WM	White matter
WWTF	Wiener Wissenschafts-, Forschungs- und Technologiefonds [Vienna Science and Technology Fund]

7.4 Abstracts

7.4.1 German Abstract

Empathie und prosoziales Verhalten sind grundlegende Fähigkeiten für den sozialen Zusammenhalt und die Bindung zwischen Menschen. Frühere Forschung konnte zeigen, dass wir den Schmerz anderer Personen nachempfinden, indem wir neuronale Prozesse aktivieren, die auch dann ablaufen, wenn wir selbst Schmerz empfinden – sogenannte ‚geteilte Repräsentationen'. Kausale Belege für solche geteilten Repräsentationen konnten durch ausgeklügelte psychopharmakologische Manipulationen wie Placebo Analgesie gezeigt werden – die Reduktion eigener Schmerzwahrnehmung durch ein Placebo-Schmerzmittel. Placebo Analgesie verringerte sowohl subjektive Empathie Bewertungen als auch Gehirnaktivität innerhalb der affektiv-motivationalen Komponente der Schmerzverarbeitung, insbesondere in der anterioren Inselrinde und im anterioren, mittleren zingulären Kortex. Während bisherige Forschung zwar bereits die Grundlage für das Verständnis der Verarbeitung von Empathie im Gehirn geschaffen hat, bleiben mehrere entscheidende Fragen zur Spezifität geteilter Repräsentationen unbeantwortet. Die vorliegende, kumulative Dissertation verfolgte einen sozialneurowissenschaftlichen, multimethodischen Ansatz, um bestehende Erkenntnisse über die neuronalen Grundlagen von Empathie und prosozialem Verhalten im Bereich Schmerz zu erweitern. Ziel der Arbeit war es, das Konzept der geteilten Repräsentationen von eigenem Schmerz und Empathie für Schmerz durch die Kombination von Placebo Analgesie mit maßgeschneiderten experimentellen Designs, psychologischen Aufgaben und funktioneller Magnetresonanztomographie zu spezifizieren. Diese Dissertation umfasst drei empirische Studien, von denen zwei bereits veröffentlicht sind und eine bei einer wissenschaftlichen Fachzeitschrift eingereicht wurde. In Studien 1 und 2 wurde mithilfe zweier klassischer Empathie Aufgaben untersucht, ob geteilte Repräsentationen neben der affektiv-motivationalen auch die sensorisch-diskriminative Komponente der

Schmerzverarbeitung nutzen. Die Ergebnisse replizierten überlappende Hirnaktivität in der affektiv-motivationalen Komponente bei eigenem Schmerz und Empathie für Schmerz, gaben aber keine Hinweise auf geteilte, somatosensorische Repräsentationen. Dies deutet darauf hin, dass Empathie für Schmerz eher auf dem Teilen des allgemeinen affektiven Zustands Anderer beruht als auf dem spezifischen somatosensorischen Zustand. Studie 3 untersuchte darauf aufbauend, ob die schmerzsenkende Wirkung von Placebo Analgesie neben einer Verringerung der Schmerzempathie auch das prosoziale Verhalten beeinflusst. Wenn Versuchspersonen die Schmerzen einer anderen Person durch körperliche Anstrengung reduzieren konnten, trafen Personen unter dem Einfluss von Placebo Analgesie weniger prosoziale Entscheidungen (abhängig davon, wie sehr sie in einer bestimmten Situation helfen konnten), halfen weniger schnell und strengten sich beim Helfen weniger an als Kontrollpersonen mit unveränderter Schmerzempfindlichkeit. Darüber hinaus waren subjektive unangenehme Gefühle beim Beobachten der anderen Person, welche schmerzhafte elektrische Stimulationen bekam, mit mehr prosozialen Entscheidungen assoziiert. Diese Ergebnisse zeigen, dass eine verringerte Schmerzempfindlichkeit nicht nur die Art und Weise beeinflusst, wie wir den Schmerz anderer wahrnehmen und teilen, sondern auch unsere soziale Motivation und Verhalten. Die Ergebnisse dieser Arbeit sind wichtig, um besser zu verstehen, wie Empathie im Gehirn entsteht, verarbeitet wird und wie dies mit prosozialem Verhalten zusammenhängt.

7.4.2 English Abstract

Empathy and prosocial behavior are crucial skills for social cohesion and bonding among individuals. Previous research has highlighted that we come to empathize with the pain of other individuals by activating neural processes that are also engaged when we feel pain ourselves – so-called 'shared representations'. Causal evidence for such shared representations has been shown through sophisticated psychopharmacological manipulations such as placebo analgesia – the downregulation of one's own pain by means of a placebo painkiller. Placebo analgesia reduced both subjective ratings for pain empathy as well as decreased neural activation in the affective-motivational component of pain processing, namely in anterior insula, and anterior midcingulate cortex. While this research already set the basis for understanding how empathy is processed in the brain, several crucial questions that concern the specificity of shared representations between first-hand and empathy for pain remain unanswered. The present dissertation adopted a multi-method, social neuroscience approach to advance existing insights into the neural underpinnings of empathy and prosocial behavior in the domain of pain. It aimed to specify and extend the shared representations account of first-hand pain and empathy for pain, by combining placebo analgesia with tailored experimental designs, psychological tasks, and functional magnetic resonance imaging. This PhD thesis comprises three empirical studies, two already published and one submitted to a peer-reviewed journal. Studies 1 and 2 explored whether shared representations extend beyond the affective-motivational to the sensory-discriminative component of pain processing using two classic empathy for pain paradigms. The results replicated an overlap brain activity in the affective-motivational component but showed no evidence for somatosensory sharing. This suggests that empathy for pain may rely more on sharing another's general affective, compared to their specific somatosensory state. Subsequently, Study 3 investigated whether the pain-reducing effect of placebo analgesia

reaches beyond pain empathy up to influencing prosocial behavior. When given the opportunity to reduce the pain of another individual by exerting physical effort, people under the influence of placebo analgesia made fewer prosocial choices (dependent on how much they could help in a given situation), helped less quickly, and exerted less physical effort when helping, compared to control participants with unaltered pain sensitivity. Moreover, self-reported unpleasantness when observing the other person getting painful electrical stimulation was associated with more prosocial choices. These results showed that reduced pain sensitivity not only influences how we perceive and share others' pain, but also critically affects our social motivation and behavior. The findings of this thesis are important for further understanding how empathy is represented in the brain and how it is connected to prosocial behavior.

7.5 Academic Curriculum Vitae

Nationality:	German	Homepage:	www.helenahartmann.com
Address:	Eerste Ringdijkstraat 4	ORCID:	0000-0002-1331-6683
	1097 BC Amsterdam, NL	Google Scholar	
Phone:	+43 660 5056363	Twitter	
Email:	helena.m.hartmann@gmail.com	LinkedIn	

Academic Working Experience

01/2021 – 03/2022 Pre-doctoral researcher (NIN, Amsterdam)

- Social Brain Lab, Netherlands Institute for Neuroscience
- Project “Another’s pain vs. my gain: The causal role of the prefrontal cortex in prosocial decision-making”

03/2017 – 12/2020 Pre-doctoral researcher (University of Vienna, Vienna)

- Department of Cognition, Emotion, and Methods in Psychology Social, Cognitive and Affective Neuroscience (SCAN) Unit
- Dissertation and project “Age-related changes of brain correlates underlying affective touch and interoception: A cross-sectional fMRI study”

02/2016 – 02/2017 Pre-doctoral researcher (University of Vienna, Vienna)

- Department of Clinical and Health Psychology
- Project "Family Development over the Lifespan"

02/2016 – 05/2016 Pre-doctoral internship (University of Vienna, Vienna)

- Department of Clinical and Health Psychology
- Project “The Central European Network on Fatherhood (CENOF)”

Education

10/2017 – present Doctoral Studies in the Natural Sciences (University of Vienna)

- Department of Cognition, Emotion, and Methods in Psychology, Social, Cognitive and Affective Neuroscience (SCAN) Unit
- Doctoral program “Cognition and Communication”
- Dissertation: “Another’s pain in my brain: Clarifying the specificity of shared representations of pain in empathy and prosocial behavior” (Supervision: Prof. Claus Lamm)

10/2014 – 05/2017 Master of Science, Clinical and Biological Psychology (University of Vienna)

- Master thesis: "Emotional Egocentricity Bias during Social Interactions in Autism-Spectrum-Disorder: Behavioral and Neurophysiological Evidence" (Supervision: Prof. Giorgia Silani)
- graduated with distinction (1.0)

10/2011 – 07/2014 Bachelor of Science, Psychology (University of Vienna)

Psychological Working Experience

05/2020 – present Psychologist / Social Neuroscientist (MyMind GmbH, Vienna)

- Startup developing Brain Hero®, a neurofeedback game to improve concentration levels and relaxation capabilities in individuals with autism spectrum disorder

04/2015 – 07/201 Personal recreational assistance (Vienna)

- Regular supervision of a patient with autism spectrum disorder

11/2014 – 04/2015 Internship (Autistenzentrum Arche-Noah, Vienna)

- Work in two day-care facilities for adolescents and adults with autism spectrum disorder

09/2010 – 08/2011 Internship (Bezirkskrankenhaus, Bayreuth)

- Psychiatric Clinic for Children and Adolescents (children's ward)

Funding and Honors

2021 VDS CoBeNe Finalization Grant (6750 €)

Marietta Blau-Grant, Austrian Agency for International Cooperation in Education and Research (OeAD, salary of 1540 € per month for a one-year abroad stay)

2020 Giselher-Guttmann-Prize for outstanding scientific work in the field of neuropsychology, Society for Neuropsychology Austria/GNPÖ (500 € and a one-year membership at the GNPÖ)

JUWI COVID fellowship, Young-Scientist-Fund, University of Vienna (1680 €)

Participant reimbursement grant, Vienna Cognitive Science Hub, University of Vienna (400 €)

2019 Poster prize at the 9th IMPRS Neurocom Summer School in Leipzig for the poster "Effects of local placebo analgesia on somatosensory responses during first-hand and empathy for pain" (185 €)

Travel scholarship, Young-Scientist-Fund, University of Vienna (300 €)

2018 – 2020 Doc:muv Career Development Program for early-stage researchers, Department for Gender Equality & Diversity, University of Vienna

2018 BestMasters (publication of the master thesis at Springer Publishing)

	Travel scholarship, Young-Scientist-Fund, University of Vienna (400 €)
	Top 10 in the University of Vienna photo competition "My Research in one Picture"
2017 – 2020	Uni:docs Fellowship Program for Doctoral Candidates, University of Vienna (competitive grant with 14 % acceptance rate; paid 3-year position and an additional total grant of 18.000 €)
2016	Promotional scholarship for the conduction of the Master Thesis, University of Vienna (2400 €)
2013 – 2017	Four scholarships during the Bachelor and Master for excellent academic achievements, University of Vienna (in total ca. 3000 €)

Teaching and Supervision Experience

2021	Graduate School Neurosciences Amsterdam Rotterdam (ONWAR) course on Transcranial Magnetic Stimulation for PhD students.
	Lab-internal workshop on RMarkdown and GitHub together with Leonardo Cerliani, Social Brain Lab, Netherlands Institute for Neuroscience, Amsterdam.
2020	Guest talk in Master seminar Development and Education – Developmental psychology from a pop science perspective about "Science for Everyone! Science communication for beginners" (WS 2020, slides on OSF).
2019 – 2020	Guest talks in Bachelor seminar Decision Neuroscience about "Doing Good/Open Science" (SS 2019, SS 2020; talk on YouTube).

Theoretical and practical supervision of multiple interns at Bachelor and Master level, as well as co-supervision of six master theses together with Univ.-Prof. Claus Lamm:

- „Specifying the neural underpinnings of placebo empathy analgesia" (Anna Köstler, graduated 10/2019)
- „Der Einfluss von Meditation auf Empathie und Mitgefühl und die zugrundeliegenden Hirnareale – ein Review" (Emma Skarke, graduated 11/2019)
- „Empathy for pain paradigms and spatial specific placebo analgesia: evidence for personal distress?" (Fabian Franken, graduated 12/2019)
- „To respond or not to respond: Effects of empathy and brain structure on placebo responding" (Magdalena Banwinkler, graduated 11/2020, currently a PhD student in Cologne)
- „The association between interoceptive abilities and empathy" (Elisabeth Löffler, planned graduation 2022)
- "Inter-individual differences and the causal role of the dorsolateral prefrontal cortex in human social decision making" (Ivar Rambags, planned graduation 2022)

Professional Affiliations & Services

Present	Social Media Committee for the Social Brain Lab, the Society for Social Neuroscience, FORRT and the Feminist Alliance Book Club
	FORRT (Framework for Reproducible Research Training) Collaborator

	Co-organization of the European Society for Cognitive and Affective Neuroscience (ESCAN) conference in Vienna (2022), and the annual meetings Psychology and the Brain (PuG) of the DGPs and the DGPA as part of the Young Scientists, section Biopsychology and Neuropsychology (2021 and 2022)
	Ad-hoc peer-review (Psychiatry Research/Elsevier, Psychophysiology/Wiley, Progress in Neuropsychopharmacology & Biological Psychiatry/Elsevier, Quarterly Journal of Experimental Psychology/SAGE, International Journal of Qualitative Studies on Health & Well-being, Taylor & Francis)
	Member of the German Psychological Society (DGPs) and the section Biopsychology and Neuropsychology, the Austrian Society for Psychology (ÖGP) as well as the Association for Neuropsychology Austria (GNPÖ)
	Center of Open Science (COS) Ambassador and member of the DGPs interest group "Open and Reproducible Research in Biological Psychology" (IGOR)
	CoBeNe Fellow (Vienna Doctoral School - Cognition, Behavior and Neuroscience, "Sociality & Communication" program, University of Vienna)
2020 – 2021	PsyArXiv moderator
	International Association for the Study of Pain (IASP)
	European Society for Cognitive and Affective Neuroscience (ESCAN)
	Association for Neuropsychology Austria (GNPÖ)
2019 – 2020	Organization for Human Brain Mapping (OHBM)
2017 – 2020	Coordinator of the monthly Joint Group Meeting and Social Event (SCAN-Unit, University of Vienna) as well as the Lab's Twitter account
2017 – 2018	Scientific Society Autism Spectrum (WGAS)
	International Society for Autism Research (INSAR)

Scientific Outreach

2021	German article "Dein Leid ist mein Leid? Wie wir die Emotionen anderer Personen nachempfinden" at In-Mind magazine in the special issue 4/2021 "Wie verstehen wir andere besser?", German In-Mind glossary entries for „Theorie der Geteilten Repräsentationen" and „Endogenes Opioidsystem", Kaffeeklatsch mit Wissenschaft, Pint of Science Netherlands (team Amsterdam, as volunteer and host)
2020	Pint of Science Austria (Volunteer in team "Beautiful Mind" and Social Media Manager), The Aaron Halliday Podcast, 1 Million Women in STEM, Real Scientists DE, workshop at the Children's University Vienna, Interview with DiscoverPhDs, Curiosity Cake Podcast
2019	Every Little Thing Podcast
2018	Long Night of Research, Vienna

Advanced Trainings & Additional Qualifications

Present	Co-founder and -organizer of an international online book club (FemABC)
	Conducting behavioral and fMRI experiments using • Digitimer DS5 Isolated Bipolar Constant Current Stimulator • Vernier Hand Dynamometer • Local and global placebo analgesia induction (pill, cream) • Physiological measurements (electrocardiography, skin conductance)
2021	Training to conduct studies using repetitive Transcranial Magnetic Stimulation (Magstim Rapid^2) and Neuronavigation (Rogue Research)
	Certified Emergency Response Officer course / Gecertificeerd Bedrijfshulpverlener (ISO/IEC 17024:2012), NedCert, Amsterdam
2019	Two-day visit at Prof. Dr. med. Christian Büchel's lab and introduction of the PATHWAY – Pain & Sensory Evaluation System (CHEPS), Institute of Systems Neuroscience (University Medical Center Hamburg-Eppendorf)
2018	Seven-day summer school on the neuroanatomy of cognition "Visceral Mind" (Bangor University)
	Training for the use of the Eyetracking System SR Research Eyelink 1000 Plus
2017	Four-day training course on MATLAB, fMRI, and Statistical Parametric Mapping (Institute of Systems Neuroscience, University Medical Center Hamburg-Eppendorf)
	Training for "Qualified User", independent scanning using 3T Magnetom Skyra MR Siemens Scanners (University of Vienna)

Languages	German	Native tongue
	English	Fluent written and spoken
	Dutch	Basic written and spoken
IT/Statistics	Programming in MATLAB (Cogent Toolbox)	Advanced knowledge
	RStudio, RMarkdown, JASP	Advanced knowledge
	SPSS, SmartPLS	Advanced knowledge
	Statistical Parametric Mapping (SPM)	Advanced knowledge
	Python/Jupyter Notebook, FreeSurfer	Intermediate knowledge
	PHP-Code, Shell scripting (bash, tcsh)	Basic knowledge
Other	SoSciSurvey (online questionnaire platform)	Advanced knowledge
	Limesurvey, Google Forms	Advanced knowledge
	Photoshop	Intermediate knowledge
	Gorilla Experiment Builder	Basic knowledge
	PsychoPy	Basic knowledge

Preregistrations

Hartmann, H., & Lamm, C. (August 8th, 2019). *Another's pain in my social brain: The effects of placebo (empathy) analgesia on social behavior*. Public preregistration on the Open Science Framework. URLs: osf.io/g3acp and osf.io/qw3kg

Hartmann, H., Riva, F., & Lamm, C. (August 8th, 2019). *The effects of placebo analgesia on interoceptive abilities*. Public preregistration on the Open Science Framework. URL: osf.io/gh4sf

Hartmann, H., Rütgen, M., Sladky, R., & Lamm, C. (August 3rd, 2018). Another's pain in my brain: Clarifying the specificity of the effects of placebo analgesia on first-hand and empathy for pain. Public preregistration on the Open Science Framework. URLs: osf.io/uwzb5 and osf.io/h7v9p.

Publications

1. **Hartmann H.**, Forbes, P., Rütgen, M., & Lamm C. (submitted to *Psychological Science* on 24.01.2022). *Placebo analgesia reduces prosocial behavior when preventing another's pain. PsyArXiv Preprint.* https://doi.org/10.31234/osf.io/drfht
2. Parsons, S., Elsherif, M., … **Hartmann, H.** et al. (2022). A community-sourced glossary of open scholarship terms. Accepted at *Nature Human Behavior*.
3. **Hartmann, H.***, Lengersdorff, L.*, Stepnicka, P., Hitz, H., & Silani, G. (2022). Emotional ego- and altercentric biases in high-functioning autism spectrum disorder: Behavioral and neurophysiological evidence. Accepted for the special issue "Women in Psychiatry 2021: Social Cognition" in *Frontiers in Psychiatry* (* = equal contribution).
4. Azevedo, F., Parsons, S., Micheli, L., Strand, J. F., Rinke, E., Guay, S., … , **Hartmann, H.** & FORRT (2020). Introducing a Framework for Open and Reproducible Research Training (FORRT). *OSF preprint*. https://doi.org/10.31219/osf.io/bnh7p
5. **Hartmann, H.**, Riva, F., Rütgen, M., & Lamm, C. (2021). Placebo analgesia does not reduce empathy for naturalistic depictions of others' pain in a somatosensory specific way. *Cerebral Cortex Communications*, 2(3), tgab039. https://doi.org/10.1093/texcom/tgab039
6. **Hartmann, H.**, Rütgen, M., Riva, F., & Lamm, C. (2021). Another's pain in my brain: No evidence that placebo analgesia affects the sensory-discriminative component in empathy for pain. *NeuroImage*, 224, 117397. https://doi.org/10.1101/2020.05.18.101238
7. Massaccesi C., Groessing, A., Rosenberger, L. A., **Hartmann, H.**, Candini, M., Di Pellegrino, G., Frassinetti, F., & Silani, G. (2021). Neural correlates of interpersonal space permeability and flexibility in adults with autism spectrum disorder. *Cerebral Cortex*, 31(6), 2968–2979. https://doi.org/10.1093/cercor/bhaa404
8. Pownall, M., Talbot, C. V., Henschel, A., Lautarescu, A., Lloyd, K., **Hartmann, H.**, … Siegel, J. A. (2021). Navigating Open Science as Early Career Feminist Researchers. *Psychology of Women Quarterly, 0*(0), 1-14. https://doi.org/10.31234/osf.io/f9m47
9. **Hartmann, H.** (2018). *Social Interactions in Autism: Cognitive Empathy, Egocentricity and Social Pain.* Springer.
10. **Hartmann, H.** (2018). Therapeutische Maßnahmen bei Autismus-Spektrum-Störungen. In B. Rollett & U. Kastner-Koller, *Praxisbuch Autismus. Für Eltern, Lehrer, Erzieher und Therapeuten* (pp. 119 – 136). Elsevier.

In preparation:

Banwinkler, M., Lamm C., & **Hartmann, H.** (in prep). Association between long-term pain medication use and empathy/prosocial behavior.

Hartmann, H., Riva, F., Banwinkler, M., & Lamm C. (in prep). Behavioral and structural differences between placebo analgesia responders and non-responders.

Hartmann, H., Paracampo, R., Lengersdorff, L., Lamm, C., Keysers, C., & Gazzola, V. (in prep). Another's pain vs. my gain: The causal role of the prefrontal cortex in prosocial decision-making.

Invited Contributions

Hartmann, H. (2022, January). Another's pain vs. ma gain: Using rTMS to study the causal role of the prefrontal cortex in costly decision-making. Invited talk at an internal TMS meeting at the psychiatric wing of the Amsterdam Medical Center (AMC) (online).

Hartmann, H. (2021, December). *Placebo analgesia reduces prosocial behavior when preventing another's pain.* Talk at the conference of the Society for Social Neuroscience (S4SN) (online, talk on Youtube).

FORRT (2021, November). Replications and reversals in social sciences. Hackathons organized at the Association for Interdisciplinary Metaresearch and Open Science (aimos) and Psychological Science Accelerator (PSACON) conferences (online, aimos hackathon on Youtube).

Hartmann, H. (2021, October). *Geteiltes Leid? Die Effekte von Placebo-Analgesie auf Empathie für Schmerz und prosoziales Verhalten*. Talk at the conference of the Austrian Society for Neuropsychology (GNPÖ), Vienna, Austria.

Hartmann, H. (2021, June). *Preregistering an fMRI study – First experiences and lessons learned*. Talk at the methods meeting of the Institute of Systems Neuroscience, Hamburg, Germany (online).

Hartmann, H. (2021, June). *The effects of placebo analgesia on prosocial decision-making during pain avoidance.* Talk as part of the symposium "What do you desire? Multiple facets of motivation in social decision-making" organized by Lei Zhang and Helena Hartmann, European Society for Cognitive and Affective Neuroscience (ESCAN) Meeting, Budapest, Hungary (online).

Hartmann, H. (2021, June). *How does placebo analgesia affect decisions to exert effort to reduce another's pain?* Talk as part of the Posterblitz, 46th joint annual meeting Psychology and the Brain (PuG) of the Division of Biological Psychology and Neuropsychology of the German Psychological Society (DGPs) and the German Society for Psychophysiology and its Application (DGPA) (online).

Pownall, M., Talbot, C., Henschel, A., Lautarescu, A., Lloyd, K., **Hartmann, H.**, Darda, K., Tang, K., Carmichael-Murphy, P., & Siegel, J. (March 2021). *Navigating open science as early career feminist researchers.* Collaborative talk at the symposium "Open Research: A Vision for the Future" organized by the RIOT Science Club (online, talk on Youtube).

Hartmann, H. (2021, March). *Do I feel my heart beating? The effects of placebo analgesia on interoceptive abilities.* Talk as part of the symposium "From heart to brain and back: novel findings and methodological challenges in interoception research" organized by Federica Riva and Helena Hartmann, 63rd Conference of Experimental Psychologists (TeaP), Ulm, Germany (online).

Hartmann, H. (2020, November). *Another's pain in my brain: Effects of spatially-specific placebo analgesia on somatosensory responses during first-hand pain and empathy for pain.* Talk at the Science Slam at the conference of the Austrian Society for Neuropsychology (GNPÖ); Abstract published in *Zeitschrift für Neuropsychologie*, Abstracts of the 22nd yearly meeting of the GNPÖ, Vienna, Austria (online).

Hartmann, H. (2020, November). *Another's Pain in my Brain: Effects of spatially-specific placebo analgesia on somatosensory responses during first-hand and empathy for pain.* Talk at the OnNeuro virtual webinar / neuroscience lecture series (online, talk on YouTube).

Hartmann, H. (2020, November). *Another's pain in my brain: What about somatosensory shared representations in first-hand and empathy for pain?* Talk at the Affective Brains during Covid (ABC) seminar series of the Leknes Affective Brains (LAB) Lab (online).

Hartmann, H. (2019, September). *Another's Pain in my Brain: Effects of spatially-specific placebo analgesia on first-hand and empathy for pain.* Talk given at the group meeting of the Social Brain Lab (group leaders: Prof. Christian Keysers and Prof. Valeria Gazzola), Netherlands Institute for Neuroscience, Amsterdam, The Netherlands.

Hartmann, H. (2017, October). *Emotional egocentricity bias during social pain in Autism-Spectrum-Disorder (ASD): Behavioral and neurophysiological evidence*. Talk at the Science Slam at the conference of the Austrian Society for Neuropsychology (GNPÖ); Abstract published in *Zeitschrift für Neuropsychologie, 29*(1), 61, Abstracts of the 19th yearly meeting of the GNPÖ, Vienna, Austria.

Selected Posters

Hartmann, H., Forbes, P., Rütgen, M., & Lamm, C. (2021, June). *How does placebo analgesia affect decisions to exert effort to reduce another's pain?* Poster at the 46th joint annual meeting Psychology and the Brain (PuG) of the Division of Biological Psychology and Neuropsychology of the German Psychological Society (DGPs) and the German Society for Psychophysiology and its Application (DGPA) (online).

Pownall, M., Talbot, C., Henschel, A., Lautarescu, A., Lloyd, K., **Hartmann, H.**, Darda, K., Tang, K., Carmichael-Murphy, P., & Siegel, J. (February 2021). Engaging with Open Science as feminist Early Career Researchers: 6 Top Tips. Poster at the Open Science conference (online).

Hartmann, H., Riva, F., Rütgen, M., & Lamm, C. (January and March 2021). *Is your pain my pain? Effects of localized placebo analgesia on empathy for everyday painful situations*. Poster at the Society for Neuroscience (SfN) Global Connectome 2021 and the 8th MindBrainBody Symposium of the Max Planck Institute for Human Cognitive and Brain Sciences (both online).

Hartmann, H., Rütgen, M., Riva, F., & Lamm, C. (September 2020). *Another's Pain in my Brain: Effects of local placebo analgesia on somatosensory responses during first-hand and empathy for pain*. Poster at the poster gallery of the IASP Virtual Series on Pain & Expo (online).

Hartmann, H., Rütgen, M., Sladky, R., & Lamm, C. (June 2019). *Another's Pain in my Brain: Effects of local placebo analgesia on somatosensory responses during first-hand and empathy for pain.* Poster at the 9th IMPRS Neurocom Summer School, Leipzig, Germany and the 25th Annual Meeting of the Organization for Human Brain Mapping (OHBM), Rome, Italy.

Hartmann, H., Rütgen, M., Sladky, R., & Lamm, C. (June 2019). *Effects of local placebo analgesia on picture-based pain empathy*. Poster at the 25th Annual Meeting of the Organization for Human Brain Mapping (OHBM), Rome, Italy.

Sladky, R., Lengersdorff, L., Woletz, M., **Hartmann, H.**, Tik, M., Windischberger, C., & Lamm, C. (June 2019). *SweetData: a versatile open-source tool for lab data management and validation.* Poster at the 25th Annual Meeting of the Organization for Human Brain Mapping (OHBM), Rome, Italy.

Riva, F., Silani, G., **Hartmann, H.**, & Lamm, C. (June 2019*). Age-related differences in the neural correlates of social affective touch.* Poster at the 25th Annual Meeting of the Organization for Human Brain mapping (OHBM), Rome, Italy.

Massaccesi, C., Grössing, A., Hubinger, M., Rosenberger, L., **Hartmann, H.**, Candini, M., Frassinetti, F., di Pellegrino, G., & Silani, G. (June 2019). *Regulation of personal space by social interactions in adults with autism: an fMRI study*. Poster at the 25th Annual Meeting of the Oragnization for Human Brain mapping (OHBM), Rome, Italy.

Hartmann, H., Hitz, H. M., Stepnicka, P., Lengersdorff, L., & Silani, G. (May and November 2018). *Social pain and emotional egocentricity in high-functioning Autism-Spectrum-Disorder (ASD): Behavioral and neurophysiological evidence*. Poster at the International Society for Autism Research (INSAR) Annual Meeting, Rotterdam, The Netherlands, and the 11th Scientific Meeting for Autism Spectrum Conditions (WTAS), Frankfurt, Germany.

Hartmann, H., Radl, V., Winter, B., Cholewa, A., & Rollett, B. (August 2017). *Self-regulation and well-being.* Poster at the 17th Biennial European Association for Research on Learning and Instruction (EARLI) Conference, Tampere, Finland.

Werneck, H., Rollett, B., Klinger, D., Mühlbauer, P., **Hartmann, H.**, Winter, B., & Engländer, S. (June 2017). *Family Development in the Course of Life (FIL) – an Austrian Longitudinal Project over 22 Years.* Paper at the International Couple and Family Psychology Conference "Crossroads of Couple and Family Psychology: A Foundation for Future Real World Practice", Evanston/Illinois.