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„The role of uncertainty during pain anticipation in major depressive disorder: An EEG study "

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Abstract

Theoretical background: Major depressive disorder (MDD) has been associated with altered neural activations during the anticipation of pain as well as intolerance of uncertain situations. However, pain anticipation in MDD has not yet been investigated with electroencephalography (EEG). Besides, little is known about the effect of antidepressant medication on pain anticipation in MDD. Therefore, an EEG study was conducted with a focus on the stimulus-preceding negativity (SPN), an event-related potential (ERP) associated with the anticipation of emotionally salient stimuli, which can distinguish between early and late phases of anticipation.

Methods: 31 (19 females) with acute MDD and 31 (21 females) matched healthy control subjects (HCs) underwent a pain anticipation paradigm while EEG was recorded (T1). A visual cue indicated an upcoming painful or non-painful electrical stimulus that occurred with certainty or uncertainty (50% chance of occurrence of a painful stimulus). Further, pain- and uncertainty-related personality dimensions were assessed. Subsequently, the MDD group underwent treatment with escitalopram for 12 weeks, which was succeeded by a second EEG measurement (T2).

Results: (1) In both groups early and late SPN amplitudes were most pronounced in uncertain trials. (2) In both groups early SPN amplitudes were more pronouncedat T2. (3) On a trend level, late SPN amplitudes were more pronounced in the MDD group. No further differences in early and late SPN amplitudes were found between the groups. (4) Pain thresholds did not differ between groups and measurements. (5) Compared to HCs, the MDD group scored higher on pain catastrophizing and intolerance of uncertainty.

Conclusion: Results mainly follow a certainty-related logic, indicating that uncertainty affects pain anticipation independent from psychopathology and anticipation phase. The fact that the only significant time effect was observed in both groups suggests that antidepressant treatment did not affect anticipation processes, but that the time effect is rather specific to the early SPN component. Findings of altered cognitive evaluation of pain- and uncertainty-related constructs in MDD, accompanied by a lack of ERP and behavioral differences between the MDD and HC group, point to a maladaptive mechanism in depression. However, limitations of the study may as well have an impact on the lack of group differences.

Key words: Major depressive disorder, pain anticipation, uncertainty, antidepressant medication, EEG, stimulus-preceding negativity

Zusammenfassung

Theoretischer Hintergrund: Unipolare Depression wurde sowohl mit einer modifizierten neuronalen Aktivierung während der Antizipation von Schmerz, als auch mit der Intoleranz gegenüber unsicheren Situationen assoziiert. Jedoch wurde Schmerzantizipation in unipolarer Depression bisher nicht mittels Elektroenzephalographie (EEG) untersucht. Außerdem ist der Effekt von Antidepressiva auf Schmerzantizipation bei depressiven PatientInnen noch unklar. Daher wurde eine EEG Studie mit Fokus auf der sogenannten *stimulus-preceding negativity* (SPN) Komponente vollzogen. Dabei handelt es sich um ein ereigniskorreliertes Potential (EKP), das mit der Antizipation emotional salienter Stimuli in Verbindung steht und das zwischen frühen und späten Antizipationsphasen unterscheiden kann.

Methoden: 31 (19 Frauen) PatientInnen mit akuter unipolarer Depression und 31 (21 Frauen) vergleichbare gesunde Kontrollpersonen führten eine Schmerz-Antizipations-Aufgabe durch während EEG gemessen wurde (T1). Ein visueller Hinweisreiz deutete auf einen schmerzhaften oder nicht-schmerzhaften elektrischen Reiz hin, der mit Sicherheit oder Unsicherheit (50% Wahrscheinlichkeit eines schmerzvollen Reizes) übermittelt wurde. Außerdem wurden schmerz- und unsicherheitsspezifische Persönlichkeitsdimensionen erfasst. Anschließend unterzog sich die PatientInnengruppe einer 12-wöchigen Behandlung mit Escitalopram, worauf eine zweite EEG Messung folgte (T2).

Ergebnisse: (1) In beiden Gruppen waren frühe und späte SPN Amplituden in unsicheren Durchgängen am stärksten ausgeprägt. (2) In beiden Gruppen waren frühe SPN Amplituden in T2 am stärksten ausgeprägt. (3) Ein Trendeffekt für stärker ausgeprägte späte SPN Amplituden in der PatientInnengruppe wurde gefunden. Es gab keine weiteren Unterschiede in frühen und späten SPN Amplituden zwischen den Gruppen. (4) Schmerzreizschwellen unterschieden sich nicht zwischen den Gruppen und Messungen. (5) Verglichen mit der Kontrollgruppe, erreichte die PatientInnengruppe höhere Ausprägungen bei Schwarzmalen von Schmerz und der Intoleranz von Unsicherheit.

Schlussfolgerungen: Die Ergebnisse folgen hauptsächlich einer sicherheitsbezogenen Logik. Sie implizieren, dass Unsicherheit Schmerzantizipation unabhängig von Psychopathologie und der Antizipationsphase beeinflusst. Da der einzige signifikante Zeiteffekt in beiden Gruppen gefunden wurde, kann davon ausgegangen werden, dass die Behandlung mit Antidepressiva keinen Effekt auf Antizipationsprozesse hatte. Die beobachtete veränderte kognitive Evaluation von schmerz- und unsicherheitsspezifischen Konstrukten bei Depression, die mit fehlenden EKP- und Verhaltenssunterschieden zwischen PatientInnen und

Kontrollgruppe einhergeht, deutet auf einen maladaptiven Mechanismus bei Depression hin. Das Fehlen von Gruppenunterschieden kann jedoch auch mit den Limitationen der Studie zusammenhängen.

Schlüsselwörter: Unipolare Depression, Schmerzantizipation, Unsicherheit, Antidepressiva, EEG, stimulus-preceding negativity

1 Introduction

"…physical pain however great ends in itself and falls away like dry husks from the mind, whilst […] nervous horrors sear the soul."
(James, 1892, p.238)

While Alice James, an American diarist and sister of psychologist William James, believed that physical pain, contrary to emotional distress, is a transient suffering, it is nowadays proven that both agonizing experiences are difficult to disentangle.

Both, physical pain sensation and Major Depressive Disorder (MDD), which is commonly characterized by symptoms like emotional distress, depressed mood and negative thoughts (American Psychiatric Association, 2013), are highly prevalent pathological states, often co-occurring and directly affecting daily functioning and satisfaction with life (Li, 2015; Lin, Yen, Chen, & Chen, 2014). In fact, more than 50% of the individuals suffering from MDD, show clinical symptoms of physical pain (Demyttenaere et al., 2006). These symptoms of clinical pain can reach from back pain and joint pain to even chronic pain states (Trivedi, 2004). Due to the high comorbidity of depression and pain and their great extent of clinical and neurobiological similarities, some researchers even refer to a "pain-depression dyad" (Goldenberg, 2010). The pain-depression relationship can be considered reciprocal, with chronic pain as causal factor for depression and depression, in turn, as predisposing factor for outbreak and chronicity of pain (Jarvik et al., 2005).

Abnormal pain processing in MDD has been associated with the maladaptive activation of a neural network relevant in pain as well as emotion modulation (Ochsner & Gross, 2005). This suggests alterations in pain-related processes in MDD to be linked to deficits in emotion regulation, which describes the process by which individuals influence intensity, duration, experience and expression of activated emotions (Gross, 2007). Apart from dysfunctional emotion regulation, MDD is characterized by cognitive biases and deficits, such as distorted information processing and impairments in attention, respectively (Murrough, Iacoviello, Neumeister, Charney, & Iosifescu, 2011). Importantly, a variety of emotional and cognitive dysfunctions observed in acute MDD persistfter treatment and in remission of the disorder (Abler, Erk, Herwig, & Walter, 2007; Haeffel et al., 2005; Vanderhasselt et al., 2012). Cognitive symptoms, for instance, persist at 39-44% of the length of remission periods (Conradi, Ormel, & de Jonge, 2011).

Regarding acute MDD, a cognitive bias that has been observed in depressive individuals is intolerance of uncertainty (IU). IU can even be described as putative vulnerability factor for depression (Yook, Kim, Suh, & Lee, 2010). IU can be defined as "a cognitive bias that affects how a person perceives, interprets, and responds to uncertain situations on a cognitive, emotional, and behavioral level" (Dugas, Schwartz, & Francis, 2004, p.835). According to Dupuy & Ladouceur (2008), individuals suffering from MDD prefer having the certainty of a negative event over the unpleasantness of dealing with an uncertain situation.

Most of the situations we face in life occur with some degree of uncertainty. Uncertainty was suggested to disturb the anticipation of an upcoming event by impeding the accuracy of outcome predictions (Penrod, 2001). Anticipation processes build on expectations, predictions or beliefs regarding future states and help predicting possible outcomes and prepare the organism for these outcomes (Bozinovski & Bozinovska, 2003).

Uncertainty does not only affect anticipation processes per se, but has been shown to play a critical role in the anticipation of pain (Brown, Seymour, Boyle, El-Deredy, & Jones, 2008). The role of uncertainty in pain-related processes is underpinned by evidence of an association of increased sensitivity to pain as well as reduced pain tolerance and uncertainty in chronic pain patients (Wright, Afari, & Zautra, 2009).

Bringing together the concepts and considerations introduced so far, the present research attempts to expand the knowledge on the relationship between pain and depression by focusing on uncertainty during the anticipation of pain in individuals with MDD and by investigating the effects of antidepressant treatment on these processes.

1.1 Pain and depression

Whereas exteroceptive senses like audition and vision convey information about the external environment of an organism, pain is regarded an interoceptive sense, since it serves the function of alarming the organism and dealing with sources and consequences of noxious input by carrying information concerning the internal body condition (Craig, 2003). Due to its innate survival value, pain is being processed throughout the neuroaxis, reaching from spinal cord to cerebral cortex (Roy, 2015).

Commonly, brain regions active during an acute pain experience are referred to as "pain matrix", which most prevalently comprises the primary (S1) and secondary somatosensory cortex (S2), insular, anterior cingulate and prefrontal cortices as well as the

thalamus (Tracey & Mantyh, 2007). The brain regions pertaining to this matrix are not only involved in experiencing pain, but also in a variety of sensory, motor and cognitive functions that are often executed in parallel (Morton, Sandhu, & Jones, 2016). Thus, pain is considered to be multifaceted in nature, combining sensory, affective and cognitive dimensions (Allaz & Cedraschi, 2015). The sensory-discriminative component of pain expresses itself in projections from the lateral thalamus to S1, S2 and the insular cortex (Bushnell et al., 1999; Morton et al., 2016). The affective-motivational component of pain is related to neural activation in the anterior cingulate cortex (ACC), anterior insula and amygdala (Knudsen et al., 2011). The cognitive-attentional component, in turn, is associated with posterior parietal and prefrontal cortices as well as subsections of the ACC that are said to differ from those that serve affective nociception (Peyron, Laurent, & García-Larrea, 2000).

In patients with MDD, abnormal neural activations in response to painful stimulation have been observed that can be linked to different components of pain. Evidence for alterations in the affective-motivational component of pain comes from the investigation of patients with fibromyalgia, a disorder characterized by chronic pain conditions. In a functional magnetic imaging (fMRI) study, hyperactivation of brain areas involved in affective pain processing, that is anterior insula and amygdala, following pressure-induced pain has been associated with comorbid MDD and depressive symptoms (Giesecke et al., 2005). In turn, findings of decreased neural activation in the lateral and medial prefrontal cortex (PFC) in response to heat pain in depressive individuals indicate abnormalities in the cognitive component of pain, since regions like the PFC have been associated with emotion regulation (Strigo et al., 2008). These findings preliminarily suggest enhanced "bottom-up" emotional processing and attenuated "top-down" modulatory processing in response to unpleasant emotional stimuli to be related to MDD (Strigo, Matthews, & Simmons, 2013).

Coming back to the "pain matrix" and considering the neural correlates of MDD, it becomes clear that brain regions associated with pain and MDD overlap to a great extent. For instance, atypical activation patterns in regions like the ACC, the medial, ventrolateral and dorsolateral PFC and amygdala are responsible for various symptoms of depression (Kupfer, Frank, & Philipps, 2012). More generally, dysfunctions in frontal-limbic networks have been considered to unite depression and chronic pain (Graham et al., 2013; Lee & Tracey, 2010). Among others, this finding suggests a biological link based on shared neural alterations to underlie the high comorbidity of depression and pain.

The close relationship between pain and depression can further be explained via neurotransmission, since the monoaminergic neurotransmitter system has been suggested as

common neural substrate of the two (Fitzgibbon, Finn, & Roche, 2016). A biochemical hypothesis of MDD postulates a depletion of monoamines in the central nervous system, which manifests itself in a deficiency of ascending serotonin and noradrenaline projecting pathways (Delgado, 2000). Conversely, descending monoaminergic pathways play a role in pain regulation by modulating neuronal responses in the spinal cord through serotonin and noradrenaline release (Jaracz, Gattner, Jaracz, & Górna, 2016). As a result, the dysfunctions in the monoaminergic pathways observed in depression may promote symptoms of physical pain (Stahl, 2002).Typically, antidepressant drugs act on the monoamine system and have therefore not only been shown to effectively treat depression, but also to have analgesic effects. Thus, monoamine-based antidepressants are now commonly used for the treatment of chronic pain, such as fibromyalgia or neuropathic pain (Fitzgibbon et al., 2016). The impact of antidepressant medication on pain and other depression-related processes will be discussed in the following section.

1.1.1 Effects of antidepressant treatment

Antidepressant drugs that elevate serotonin and noradrenaline levels by inhibiting their reuptake are said to affect both clinical and painful symptoms of depression by impeding the sensation of pain (Marks et al., 2009). For instance, treatment with duloxetine in MDD patients has been associated with an activation reduction of usually hyperactive brain regions in response to painful stimulation (López-Solà et al., 2010). In fibromyalgia patients with or without concurrent MDD, treatment with duloxetine led to a reduction of pain symptoms independent from the presence of MDD, indicating that antidepressants act on depressive and painful symptoms independently (Arnold et al., 2005). When observing the cerebral blood flow using single photon emission computed tomography in unmedicated depressive patients, increases in activation levels in brain areas related to affective and cognitive components of pain have been observed, whereas the cerebral blood flow following treatment with a selective serotonin reuptake inhibitor (SSRI) was only elevated in pain-related areas linked to cognitive processing (Graff-Guerrero et al., 2008). This suggests that antidepressants primarily act on the affective-motivational component of pain.

While these findings indicate that antidepressant medication influences pain-related processes in depressive individuals in one way or the other, the effects of antidepressant drugs reach farther, affecting emotional and cognitive domains that have been found to be abnormal

in MDD. For instance, positive effects of antidepressant medication on cognitive functions, like psychomotor speed and delayed recall have been observed in MDD, whereas cognitive control and executive function remained unaffected (Rosenblat, Kakar, & McIntyre, 2016). This is in line with evidence of deficits in executive functioning observed independently of clinical variables displaying symptom severity (Lee, Hermens, Porter, & Redoblado-Hodge, 2012), which might account for persisting deficits in cognitive domains after antidepressant treatment. Besides, deficits in the reward system observed in unmedicated MDD as indicated by reduced ventral striatum activation during gain and loss anticipation could not be found after a 6 weeks treatment with escitalopram, a commonly used SSRI. This hypoactivity of the ventral striatum associated with dysfunctional anticipation of reward and punishment was hence related to the severity of depressive symptoms (Stoy et al., 2012).

As mentioned before, antidepressant treatment leads to a reduction of depressive symptoms, especially for patients with severe baseline symptomatology (Fournier et al., 2010). Thus, investigating remitted MDD (rMDD) can support research on the effects of antidepressant medication, since rMDD is characterized by a strong reduction or even absence of depressive symptoms (Fournier et al., 2010). In order to examine the cognitive control over emotional conflict, Vanderhasselt and colleagues (2012) used a cued emotional conflict task in rMDD and healthy control subjects (HC), which resulted in a lack of differences between the rMDD and HC group during the anticipation of conflict. However, the authors have found reduced cognitive control over negative emotional stimuli in rMDD compared to HCs. This points to persisting deficits in emotion regulation in remission of MDD, which is supported by findings of more negative cognitive styles in rMDD compared to never-depressed individuals (Haeffel et al., 2005). While Vanderhasselt et al. (2012) could not find differences in the anticipation of conflict between rMDD patients and healthy individuals, indicating a normalization of dysfunctional anticipation processes in remission of MDD, an fMRI study with post-acute MDD patients on stable medication did reveal increased dorsal amygdala activation during the anticipation of negative emotional stimuli. Further, depression scores correlated with ventral amygdala activation associated with the anticipation of negative emotional stimuli (Abler et al., 2007).

Another neuroimaging study with rMDD patients revealed enhanced activation in fronto-limbic regions during the anticipation of reward (Ubl et al., 2015). Additionally, rMDD has been associated with hypoactivation of PFC subregions while processing unpleasant emotional pictures (Kerestes et al., 2012). All in all, dysfunctional emotion regulation and cognitive deficits underpinned by abnormal neural activations in associated brain regions

seem to remain in remission of MDD. Although findings regarding the anticipation of gain, loss and emotional conflict, point to a normalization of primarily abnormal anticipation processes following antidepressant medication, converging evidence suggests that dysfunctions in affective as well as cognitive processes persist in post-acute or remitted MDD phases, especially in terms of emotionally salient and unpleasant stimuli. Since pain can be far more emotionally obtrusive than pictures of sad faces or monetary loss, it is here therefore proposed that abnormal anticipatory responses to pain suggested in acute MDD can still be observed after depressive symptom reduction via antidepressant treatment. This could be supported by consistently observed abnormalities in serotonergic neurotransmission in recovered depressed patients, suggesting that abnormal pain-related processes might remain altered after treatment with antidepressant drugs (Bhagwagar & Cowen, 2008). Findings of unchanged pain thresholds after electroconvulsive therapy in depressive patients despite a significant improvement of depressive symptoms indicate pain-related processes to remain unchanged across stages of depressive symptomatology (Gormsen et al., 2004). In the next section research on pain perception in MDD will be outlined.

1.1.2 Pain perception in MDD

A common behavioral method for measuring pain perception is the assessment of pain thresholds. Despite the fact of observed abnormalities in pain-related processing in depression, findings on pain thresholds in depressive patients remain inconsistent. On the one hand, a variety of studies applying hot or cold painful stimuli or painful electric stimulation to the skin have found increased pain threshold in depressive individuals, that is reduced sensitivity to pain or hypoalgesia (Bär et al., 2005; Schwier, Kliem, Boettger, & Bär, 2010; Terhaar et al., 2011). On the other hand, hyperalgesia as indexed by decreased pain thresholds has been found in patients with MDD in response to ischaemic muscle pain (Bär et al., 2005; Terhaar et al., 2011). Other studies again have found thresholds and pain sensitivity in MDD patients to be comparable to those of healthy subjects (Klauenberg et al., 2008; Piñerua-Shuhaibar et al., 1999).

Consequently, MDD can generally be associated with decreased perception of phasic superficial pain applied to the skin and transmitted via A-delta fibers and enhanced sensitivity towards “deep somatic” pain transmitted via C-fibers. According to Lautenbacher & Krieg (1994), a broad impairment of the sensory system in depression leads to “a hypolgesia to

phasic experimental pain due to diminished transmission and processing; and a hyperalgesia to tonic experimental pain and clinical pain due to insufficient activation of pain inhibitorysystems" (Piñerua-Shuhaibar et al., 1999, p.125). Hence, the inconsistencies regarding pain perception in depression might arise from differences in the modalities of painful stimulation (Thompson, Correll, Gallop, Vancampfort, & Stubbs, 2016).

1.1.3 Factors influencing the pain experience

Aside from the previously discussed dependence of pain perception on the underlying pain modality, a variety of other factors has been shown to influence the pain experience. These factors reach from neural pathways, cognitive and affective processes to situational influences.

The so-called descending pain modulatory system arising from the brainstem has been suggested to be a main source of generalized pain modulation, since it enables the regulation of nociceptive information to either facilitate or inhibit pain. Evidence points to an involvement of the brainstem in the attentional modulation of pain due to anatomical connections of the brainstem with cortical regions (Tracey & Mantyh, 2007). Attention was further said to influence sensory processing in S1 and insular cortex via the fronto-parietal attentional orienting system, while emotions act on ascending nociceptive information through descending mechanisms concentrated around the periaqueductal gray (Bushnell, Čeko, & Low, 2013). At a neural level, boundaries between emotional and attentional sources of pain modulation are unclear, because both affect ascending nociceptive information through descending modulatory pathways (Roy, 2015; Tracey et al., 2002). Due to the "highly integrated nature of the pain processing system" (Roy, 2015, p.48) unique effects of emotion and cognition on pain-evoked responses are hard to disentangle (Ploner, Lee, Wiech, Bingel, & Tracey, 2011).

Despite the neural overlap between emotional and cognitive sources of pain modulation, emotions and cognitions may still have differential impact on the pain experience. Regarding emotions, a study using laser-evoked potentials has found processing of affective images to inhibit pain-related cortical processing (Ring, Kavussanu, & Willoughby, 2013). However, affective images might not be as emotion-evoking as clinical states of fear, anxiety and depression, which have been suggested to increase pain and fuel negative cognitions (Linton & Shaw, 2011). A cognitive process representing a prerequisite for experiencing pain is

attention addressed to the noxious stimulus. Even though MDD has been convergingly linked to enhanced attentional allocation toward negative stimuli (Murrough et al., 2011), findings from unconscious processing revealed that depressed individuals were not more likely to direct their attention toward negative stimuli, but once focused had difficulties in shifting attention away from them (Joormann & Quinn, 2014).

Next to attention, higher cognitive functions such as beliefs, attitudes and expectations might enhance pain, whilst cognitive sets, such as pain-related catastrophizing, can modulate the pain experience by impairing the flexibility in coping with pain (Linton & Shaw, 2011). Pain-related catastrophizing has consistently been linked to increased pain severity, sensitivity and physical dysfunction in chronic pain patients (Edwards et al., 2011), and hence has been considered a reliable predictor of the pain experience and even risk marker for pain-related outcomes (Geisser, Robinson, & Riley, 1999; Quartana, Campbell, & Edwards, 2009). Pain catastrophizing has been defined as "exaggerated negative mental set brought to bear during actual or anticipated pain experience", comprising the dimensions magnification, rumination and helplessness (Sullivan et al., 2001b, p.53). Neuroimaging evidence suggests that pain catastrophizing is linked to the extent of neural activation induced by painful stimulation and that activated brain regions are likewise involved in attentional and emotional dimensions of pain, indicating that catastrophizing modulates pain perception by acting on anticipation and attention and by amplifying emotional responses to pain (Gracely et al., 2004). This is in line with an observed influence of pain catastrophizing on mood (Turner, Mancl, & Aaron, 2004) as well as depressive symptoms suggesting an enhanced pain experience and emotional distress in response to pain (Sullivan, Rodgers, & Kirsch, 2001a). Findings of a significantly shared variance of pain-related catastrophizing and constructs pertaining negative affect, such as depression, anxiety or worry, promotes a relationship between catastrophizing and depressive disorders (Quartana et al., 2009). Conversely, mood regulation and constructs of positive affect like optimism have been found to be inversely related to depression (Hansenne & Bianchi, 2009; Scheier, Carver, & Bridges, 1994).

Sullivan and colleagues (2001a) have found the relation between catastrophizing and pain on the one hand, and emotional distress on the other, to be partially mediated by pain expectancies. Generally, expectations of future outcomes of an event represent anticipatory processing, which has likewise been shown to be abnormal in depression.

1.2 Anticipation and depression

Anticipation of future events is critically involved in emotion processing (Phillips, Drevets, Rauch, & Lane, 2003). In line with dysfunctional emotion processing in depression, anticipation processes have also been shown to be altered in MDD (Herwig et al., 2010), playing a critical role in development and maintenance of the disorder (Beck, Rush, Shaw, & Emery, 1979). For instance, MDD has been associated with a negative affective bias during the anticipation of negative emotional images (Abler et al., 2007; Herwig et al., 2010). However,, evidence for impaired anticipation processes in MDD reaches beyond the investigation of negative emotional images to much more salient stimuli like pain.

1.2.1 Pain anticipation in MDD

In healthy individuals pain anticipation can be regarded a highly adaptive process; for instance, we learn to avoid touching a hot iron at a very early age. Anticipation was shown to be characterized by a pre-activation of event-specific brain areas (Brunia, 1999), which is supported by findings of coinciding neural activations during pain anticipation and painful stimulation itself (Price, 2002). On a neural basis, pain anticipation has been associated with increased neuronal activation levels in contralateral S1, bilateral ACC, insular cortices and medial PFC, which corresponds to brain regions comprising the "pain matrix" (Porro et al., 2002).

In pathological states like chronic pain or depression, however, anticipating pain can become maladaptive and might be accompanied by anxiety-related emotions (Tracey & Mantyh, 2007). This is in accordance with neuroimaging evidence of abnormal pain anticipation in MDD, commonly characterized by alterations in emotion-relevant brain regions. Compared to HCs, even stronger haemodynamic responses in limbic and paralimbic regions such as amygdala, anterior insula and dorsal ACC have been observed in MDD patients during the anticipation of heat pain, supporting the conception of MDD as disorder of rather dysfunctional emotional anticipatory processing (Strigo, Simmons, Matthews, Craig, & Paulus, 2008). A more recent fMRI study further revealed increased ventral anterior insula activity in MDD in response to painful heat stimulation (Strigo et al., 2013). Due to functional connections of the ventral subdivision of the anterior insula with amygdala and ACC, it has been associated with emotional processing (Cauda et al., 2010). In depressive individuals, Strigo et al. (2013) have further observed an increased functional connectivity of the dorsal

subdivision of the anterior insula with the posterior thalamus and an attenuated functional connectivity with the right inferior frontal gyrus. Taken together, these findings promote the view of increased bottom-up emotional processing and attenuated top-down modulatory processing of emotionally salient and unpleasant information in depression (Hamilton et al., 2012; Strigo et al., 2013).

Whereas pain anticipation in MDD has been thoroughly studied using fMRI, findings from other neuroimaging techniques, like electroencephalography (EEG), are limited. Regarding the anticipation of reward, however, EEG evidence has linked MDD to reduced reward anticipation, manifested via frontal EEG asymmetry (Nelson, Shankman, & Proudfit, 2014). This hyporesponsivity of the reward system in MDD is supported by fMRI data indicating reduced reward-related striatal activity during reward anticipation (Smoski et al., 2009). Gorka, Phan & Shankman (2015) have shown EEG and fMRI measures of reward anticipation to converge, indicating that both measures capture coinciding mechanisms. This gives rise to the assumption that fMRI evidence for pain anticipation in MDD can equally be complemented by EGG data capturing anticipatory responses to pain in depressive individuals. This, in turn, is supported by the contention that one of the event-related potentials (ERP) involved in pain anticipation, the so-called stimulus-preceding negativity (SPN), is similarly involved in reward anticipation (Brunia, Hackley, van Boxtel, Kotani, & Oghami, 2011).

1.2.2 Stimulus-Preceding Negativity

Due to its high temporal resolution, EEG is a favorable method for the investigation of brain responses that occur within milliseconds, like processes of expectation and anticipation (Morton et al., 2016).

Slow cortical potentials, sometimes referred to as anticipatory slow waves, have been associated with anticipation processes when measuring EEG. In experimental settings, three types of anticipatory slow waves can be distinguished: the Bereitschaftspotential, elicited prior to voluntary movement; the contingent negative variation (CNV), inducing a speeded-up response to an imperative stimulus; and the SPN, a non-motor negative deflection evoked prior to stimuli conveying relevant information (Brunia, van Boxtel, & Böcker, 2012). According to Brown (2017), CNV and SPN amplitudes exhibit a variety of similarities, such as the separation into early and late phases of anticipation. Given the stability of CNV

amplitudes observed over time (Kropp, Kiewitt, Göbel, Vetter, & Gerber, 2000), SPN amplitudes are also supposed to remain stable over time.

Despite an association of the SPN component with different types of stimuli, the negative deflection was most prominently observed in response to affective stimuli, hence representing emotional anticipation. Consequently, these different types of SPN component variations are associated with distinct scalp distributions with a right anterior representation of the affective SPN (van Boxtel & Böcker, 2004). Regarding its neural origin, the insular cortex has consistently been hypothesized as main physiological source of the SPN component, with its ventral anterior and dorsal anterior subdivisions being linked to emotion and attention processing, respectively (Brunia et al., 2011; Kotani et al., 2015). However, a more recent source analysis has identified a variety of brain regions outside the insular cortex to represent physiological origins of the SPN component, indicating that the component arises from brain regions involved in reward expectation and learning, the salience network, interoception, as well as regions related to arousal (Kotani et al., 2015). This leads to the conception that numerous brain functions related to anticipation processes are involved in the expression of the SPN component. In support of the affective connotation of the SPN component, a study on the effects of positive and negative emotions on a pre-feedback SPN has revealed a larger deflection in response to emotional stimuli of either valence compared to neutral stimuli with a right-hemispheric preponderance of the feedback-specific SPN (Kotani, Hiraku, Suda, & Aihara, 2001).

Due to the high emotional valence of pain, the SPN component has likewise been observed during the anticipation of painful stimulation. In order to accurately capture anticipatory responses to painful heat stimuli of different intensities, Brown and colleagues (2008) have distinguished early and late phases of anticipation with a temporal range of 500ms to 1000ms after a visual anticipation cue and 500ms to 0ms prior to stimulus onset, respectively. The authors found scalp distributions for early and late anticipation to differ with most negative early SPN amplitudes at fronto-central sites and most negative late SPN amplitudes at more central scalp sites. These early and late phases were thought to reflect distinct processes of pain anticipation. Whereas early anticipatory activity might reflect affective-motivational processes, late responses are possibly involved in immediate and more cognitive top-down preparatory mechanisms (Brown et al., 2008; Seidel et al., 2015). Compared to non-painful stimulation, Brown et al. (2008) found expectation of a painful stimulus to elicit a larger anticipatory response in late, but not in early anticipation. The study further investigated the effect of uncertainty of the expectation of pain on neural mechanisms

of anticipation, which resulted in a lack of differences between certain and uncertain anticipation conditions. Conversely, Seidel and colleagues (2015) did find an effect of uncertainty during pain expectation on neural mechanisms of anticipation, which will be addressed in the following section.

1.2.3 Uncertainty during pain anticipation

In a combined fMRI and EEG study, Seidel et al. (2015) investigated the effect of uncertainty on anticipatory responses to pain in healthy individuals. Uncertainty was generated by a visual cue announcing the upcoming electrical stimulation as certainly painful, certainly non-painful or uncertain with 50% chance of occurrence of a painful stimulus. During an early anticipation phase following the visual cue, uncertain anticipation evoked increased neural activity in higher visual processing areas and most negative SPN frontal SPN amplitudes compared to certain pain conditions. This points to an involvement of uncertainty in affective anticipation processes with a higher engagement of visual attention. For a late anticipation phase preceding actual stimulation, SPN amplitudes were most pronounced for certain pain with a centro-parietal minimum accompanied by specific pain-related somatosensory brain activity. This suggests pain-related preparation processes to occur when anticipating a predictable painful stimulus only. Taken together, these findings support the view of early anticipation reflecting early attentional and affective-motivational processing, which can be significantly affected by uncertainty during pain expectancy. Late anticipation in turn seems to express preparatory- and modulatory mechanisms that are most prominent when upcoming painful stimulation is certain.

While a major contribution of uncertainty to anticipation processes in healthy individuals was herewith demonstrated, uncertainty has further been suggested as risk factor for distinctive psychiatric disorders (Penrod, 2001). Since individuals who are intolerant of uncertainty tend to overestimate the possibility of negative events and consider unpredictability as stressful and anxiety-provoking, they easily experience negative affect (Yook et al., 2010). The tendency for experiencing negative affect again, is a prominent characteristic of depression, which suggests IU to be a prevalent feature in depression. Findings of correlations between IU scores and depressive symptoms provide support for the view of IU as vulnerable cognitive factor for MDD (Yook et al. 2010).

When observing anticipation processes in depressive individuals, IU was found to mediate the relationship between MDD and attenuated reward anticipation (Nelson et al., 2014). During the anticipation of images with unknown emotional valence in MDD, neural activation patterns were found to resemble those while anticipating a certainly negative event (Herwig et al., 2010). This is consistent with models that postulate negative expectations towards the future and a pessimistic attitude towards uncertain events as cognitive feature of depression (Herwig et al., 2010; Lavender & Watkins, 2004). Importantly, the fMRI study by Herwig and colleagues (2010) further revealed that a major part of the brain regions found to be active during event anticipation positively correlated with the degree of depressive symptoms. This illustrates the relevance of investigating symptom severity in studies with clinical patients, which can be done by observing after-treatment states

Altogether, pain anticipation can be regarded abnormal in MDD. While a significant contribution of uncertainty on processes of pain anticipation has clearly been observed in healthy individuals, such an effect has to not yet been investigated in individuals suffering from MDD. Due to evidence of an impact of uncertainty on reward, as well as emotional picture anticipation in MDD and a clear association of the disorder with IU, we here postulate an effect of uncertainty on pain anticipation in depressive individuals. In order to draw possible conclusions on trait-characteristics of dysfunctional anticipation processes in MDD, the present study further compared pain anticipation before and after antidepressant treatment.

1.3 Aims and hypothesis

The aim of the present study is to further elucidate the association between depression and pain on a neurophysiological level using ERPs. Whereas pain-related processes have been more widely studied using fMRI, processes of anticipating pain in MDD remain to be clarified on a neurophysiological basis. Thus, the current study investigates pain anticipation in individuals with acute MDD and healthy control subjects whilst measuring EEG. Due to its influence on pain anticipation, the focus is set on the role of uncertainty on the anticipation process. We further aim to reveal possible changes in the anticipatory response to pain following antidepressant treatment, allowing inferences on different stages of depressive symptomatology.

Regarding pain anticipation in healthy individuals, we propose to replicate the findings of Seidel et al. (2015) in order to support the notion of uncertainty affecting pain anticipation

and to strengthen the validity of the pain paradigm applied. Specifically, early anticipation of pain is expected to be associated with uncertainty, reflecting affective anticipation processes (Böcker et al., 2001). Hence, strongest anticipatory responses are expected during uncertain pain indicated by largest early SPN amplitudes. Conversely, late anticipation is expected to be linked to certain pain as reflected by largest SPN amplitudes in a certain pain condition, expressing immediate preparatory processes (Seidel et al., 2015). Since SPN amplitudes are said to display anticipation processes, more negative amplitudes refer to a stronger extent of anticipation.

It is further hypothesized that patients with acute MDD differ from healthy individuals regarding anticipatory responses to pain. In detail, more negative SPN amplitudes in MDD patients compared to healthy subjects are expected in response to uncertain pain during early anticipation, indicating enhanced bottom-up emotional processing. Concerning late anticipation, individuals with MDD are assumed to exhibit less negative SPN amplitudes during certain pain, reflecting attenuated top-down modulatory processing (Hamilton et al., 2012; Strigo et al., 2013).

Next, the present study seeks to shed light on the impact of depressive symptom reduction or rather of antidepressant treatment on pain anticipation in acutely depressed patients. Here, it is assumed that pain anticipation processes do not change significantly in response to antidepressant treatment in MDD, because of converging evidence regarding the maintenance of emotional and cognitive deficits after treatment and in remission of MDD (Abler et al., 2007; Haeffel et al., 2005; Vanderhasselt et al., 2012). Explicitly, differences between acutely depressed non-medicated patients and healthy individuals concerning pain anticipation, that is SPN amplitudes, are expected to remain comparable after antidepressant treatment of MDD.

Additionally, we examine pain thresholds before and after antidepressant treatment in MDD patients and healthy individuals in order to include a behavioral measure of pain experience, proposing altered thresholds in MDD before and after treatment (Bär et al., 2005; Terhaar et al., 2011).

Finally, pain- and depression-related personality dimensions are assessed; firstly in order to affirm the highly supported view of a stronger expression of these personality traits in depressed compared to healthy individuals Hansenne & Bianchi, 2009; Sullivan et al., 2001a). Secondly, a relationship between relevant personality dimensions and the extent of the anticipatory response to pain is assumed, suggesting stronger anticipation to pain to be linked to more pronounced pain- and depression-related personality scores. All in all, the present

thesis aims to shed light on the association between depression and pain by focusing on processes of pain anticipation and emphasizing the role of uncertainty in these processes.

2 Methods

2.1 Participants

Participants were recruited in the context of the multimodal research cluster "MAN-BIOPSY" of the University of Vienna in cooperation with the Medical University of Vienna. For the HC group, participants were recruited via billboard advertisements. In a telephone screening exclusion criteria were determined, which included typical EEG exclusion criteria (strokes, brain lesions, neurological or high infectious diseases, diabetes or hemophilia, oversensitive skin, past or present substance abuse) as well as exclusion criteria specific to fMRI research (pregnancy, breastfeeding, metal implants). Besides, individuals who had consumed psychopharmacological medication within the past three months were excluded.

Patients with acute MDD were engaged from the psychiatric ambulance of the Vienna General Hospital. When diagnosed with MDD, patients who fulfilled the above mentioned exclusion criteria were asked to participate in the current study.

All suitable participants underwent medical examination and an interview by a trained clinical interviewer, which included the administration of the German version of the Structured Clinical Interview for DSM-IV axis I (SCID-I; First, Spitzer, Gibbon, & Williams, 2012) and axis II disorders (SCID-II; Gibbon & Spitzer, 1997). In the MDD group, the Beck Depression Inventory (BDI; Beck, Steer, & Brown, 1996) and the Hamilton Depression Scale (HAM-D; Hamilton, 1960) were used to assess the severity of depressive symptoms. Individuals who reported no current symptoms and no history of psychiatric disorders were allocated to the HC group.

Preceding the measurements, each participant provided written informed consent and received financial recompense after participation. The study was approved by the ethics committee of the Medical University of Vienna (EC number 103/2011).

The final sample of the current study consisted of 31 patients with acute MDD (19 females, 12 males) aged 19-51 years (M = 30.39, SD = 8.47) and 31 age- and gender-matched HCs (21 females, 10 males) between 21-45 years (M = 29.97, SD = 6.90). All participants were right-handed, which was assessed by the Edinburgh inventory (Oldfield, 1971) and had normal or corrected-to-normal vision.

2.2 Design & Procedure

Since the group assignment was based on the psychiatric diagnosis, the study resulted in a quasi-experimental design. Before EEG measurement, participants underwent biophysiological and fMRI measurement, which lie beyond the scope of this thesis. Further, participants had to fill out questionnaires preceding the EEG recordings, which will be described in detail in section 2.3.2. EEG was measured in the laboratory of the Social, Cognitive and Affective Neuroscience Unit of the University of Vienna.

After a first measurement (T1), the MDD group received antidepressant treatment with escitalopram for 12 weeks. BDI and HAM-D scores of the patient group were repeatedly assessed every two weeks for the length of the medication intake. The HC group remained without intervention. Following the 12 weeks of antidepressant treatment, EEG measurement was repeated for both groups (T2), resulting in a between- and within-subjects study design.

2.3 Materials

2.3.1 Task

The current study applied a cued pain-anticipation paradigm with a visual cue indicating the upcoming pain condition. Visual cues were presented on a 19“ CRT monitor (Sony GDM-F520, refresh rate 85 Hz) and consisted of a flash indicating a painful stimulus delivered with certainty (CP), a crossed-out flash signaling a non-painful stimulus delivered with certainty (CNP) and a flash with a question mark signaling an uncertain trial (UC). In the uncertain trials, painful stimulation occurred with a chance of 50%. Anticipation cues were presented for an interval of 5-10 seconds and stimulation occurred for 500ms at a variable point in time during cue presentation, hence inducing temporal uncertainty among participants. Each trial was followed by an inter-stimulus interval of approximately 10 seconds, represented by a black fixation cross on the screen. An illustration of the task is presented in Figure 1. The task consisted of four runs with 15 trials each, five trials for each condition (CP, CNP and UC) presented in a randomized order, resulting in a total of 60 trials and task duration of approximately 21 minutes.

Preceding task onset, participants underwent a standardized calibration procedure in order to determine their individual painful and non-painful stimulus thresholds. They were asked to identify one electrical stimulus as “detectable but not painful” and another one as

"painful but tolerable". On a rating scale ranging from 1 (representing a detectable sensation) to 10 (representing unbearable pain), the lower and higher stimulus corresponded to 1 and 6, respectively. Stimulation was delivered via a 7mm diameter surface electrode with a platinum pin (WASP electrode, Specialty Developments) by a DS5 Isolated Bipolar Constant Current Stimulator (Digitimer, London, UK). Before the electrode was attached to the dorsal side of the left hand, the skin was sanitized to ensure low impedance. A custom-built electronic device with a PIC18F2455 microcontroller (Microchip Technology Inc., http://www.microchip.com) and a LTC1257 digital / analog converter (Linear Technology Corporation, http://www.linear.com) generated control voltage for the electrical stimulator (DS5) and was controlled via the MATLAB stimulus presentation toolbox Cogent 2000 v1.32 (developed by the Cogent 2000 team at FIL and ICN and Cogent Graphics developed by John Romaya at the LON at the Wellcome Department of Imaging Neuroscience). Individual stimulus thresholds were delivered in relation to input values of ± 1 V and output values of ± 10 mA.

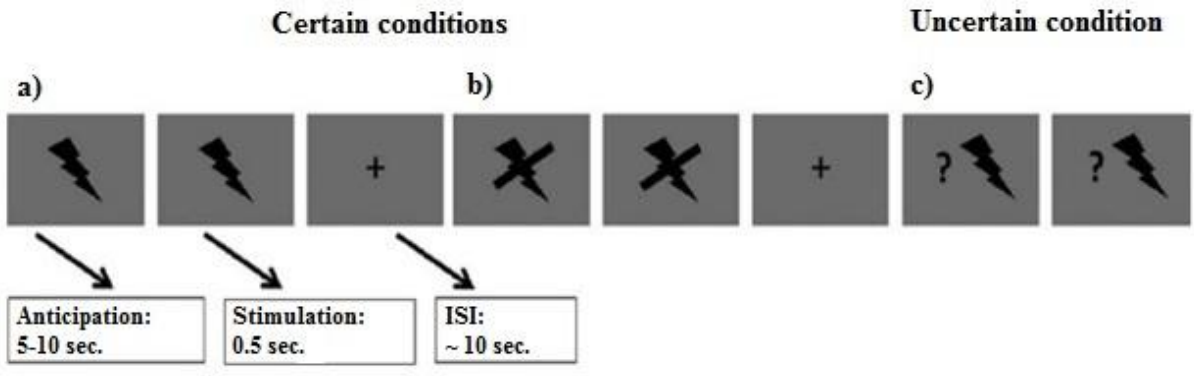

Figure 1: Illustration of the pain paradigm showing anticipation and stimulation cues of

a) certain pain, b) certain no-pain and c) uncertain pain. ISI= inter-stimulus interval.

2.3.2 Personality questionnaires

Preceding the first EEG measurement, all participants completed the online version of a series of psychological questionnaires in the laboratory, which were administered in German, assessing task- and disorder-related personality dimensions. The Pain Catastrophizing Scale (PCS; Sullivan, Bishop, & Pivik, 1995) was used to assess the level of pain-related

catastrophizing and related thoughts. The Life Orientation Test- Revised (LOT-R; Glaesmer, Hoyer, Klotsche, & Herzberg, 2008) was used for the assessment of optimism and pessimism in life. The Ungewissheitstoleranzskala (UGTS; Dalbert, 1999) was administered in order to capture tolerance of uncertainty, i.e., the ability to cope with uncertain situations.

As mentioned above, BDI and HAM-D were used to determine the severity of depressive symptoms in the MDD group. Although scores of both questionnaires were assessed every two weeks during the lengths of medication intake, we only include the scores collected before T1 and T2.

2.4 EEG recordings

EEG measurements were preceded by a standardized skin-scratching procedure to reduce the impedance between scalp and electrodes. To assure sufficient signal transmission, electrical impedances were kept below four kΩ, which was tested with an impedance meter. EGG was recorded using an elastic cap with 61 Ag/AgCl electrodes, a ground electrode for online reference placed on the forehead, and two electrodes placed above and below the left eye to measure vertical electrooculogram for vertical eye movements (model M10; Easycap GmbH, Hersching, Germany). Horizontal electrooculogram for horizontal eye movements was measured via two electrodes on the cap placed at the outside corner of each eye. Two electrodes allocated over the left and right mastoids served as offline reference.

Electrodes were arranged equidistantly according to the 10-10 system (Chatrian, Lettich, & Nelson, 1985). For signal amplification a DC amplifier setup was used (NeuroPrax, Neuroconn GmbH, Illmenau, Germany). All signals were recorded in a frequency range of DC to 250 Hz and sampled at a rate of 500 Hz for digital storage.

After application of the EEG cap and measurement of impedances, participants were seated in a sound-attenuated room equipped with a camera and an intercom system to assure the participant's safety.

3 Data analysis

3.1 ERP data

3.1.1 Preprocessing

EEG data was preprocessed offline using Matlab R2013a (The MathWorks, Inc. Natick, MA) with the EEGLAB 13.1.1b plugin (Delorme & Makeig, 2004). First, EEG data was low-pass filtered with a cut-off frequency at 30 Hz and high-pass filtered with a cut-off frequency at 0.05 Hz. Then, data was re-referenced to the average activity of the linked mastoids. In order to detect and discard artifacts reflecting eye-movements, an independent component analysis (Bell & Sejnowski, 1995) was applied to the data of each subject and artifact-afflicted components were removed from the data. In the HC group, between zero and nine components were discarded (M = 3.94, SD = 1.43). In the MDD group, between zero and seven components were discarded (M = 4, SD = 1.06).The anticipation phase was then corrected to a baseline of the mean of the last 500 ms before cue onset. Next, data was extracted into early and late anticipation phases. The early anticipation phase was segmented stimulus-locked to the onset of the visual cue with an interval of -1000 ms to 5000 ms, whereas the late anticipation phase was segmented stimulus-locked to the onset of actual stimulation with an interval of -5000 ms to 1000ms. Subsequently, a semi-automatic artifact correction was implemented, discarding trials with voltages exceeding ± 75 μV and voltage drifts of > 50 μV after visual inspection. In both groups, between zero and five trials were discarded per condition. In a few cases, a maximum of 10 trials were removed. Artifact-free trials were then averaged per participant and per condition.

To analyze early SPN amplitudes, mean amplitudes were calculated for an interval of 700 ms to 1200 ms after onset of the visual cue. Early SPN mean amplitudes were extracted for FCz (labeled R14) and the six surrounding electrode sites, which were labeled L8, L9, L12, L16, R11 and R15. For late SPN amplitudes, mean amplitudes were calculated for an interval of -500 ms to 0 ms prior to stimulus onset for CPz (labeled R24) and the six surrounding electrode sites, which were labeled L16, L17, L22, L26, R19 and R25. These intervals were chosen theory-driven on the basis of prior research at the University of Vienna (Grahl, 2013; Burkart, 2015) and after verification through visual inspection of the data.

3.1.2 Statistical analysis

For statistical analysis SPSS 21 (SPSS Inc., IBM Corporation, NY) was used. According to previous findings, early and late SPN amplitudes are most prominent at fronto-central and centro-parietal midline electrodes, respectively (e.g. Brown et al., 2008; Seidel et al., 2015). In order to avoid electrode site as factor in the statistical model and hence minimize overall factors, early SPN mean amplitudes were merged for FCz (R14) and the six surrounding electrode sites, comprising electrodes L8, L9, L12, L16, R11 and R15. For statistical analysis of late SPN amplitudes in turn, mean amplitudes were merged for CPz (R24) and the six surrounding electrode sites, comprising electrodes L16, L17, L22, L26, R19 and R25. This resulted in one mean amplitude value for the early and late SPN component per participant, and per condition.

Preceding statistical analysis of the ERP data, a winsorising procedure was performed to account for potential outliers (Wilcox, 2011). The procedure was applied to the mean SPN amplitudes per group for each participant and condition, replacing all mean amplitudes that exceed the "value corresponding to the 75th percentile plus 1.5 times the interquartile range with the maximum [mean amplitude] within this range in the corresponding condition. Accordingly mean [amplitudes] lower than 25th percentiles minus 1.5 times the interquartile range were replaced with the minimal [mean amplitude] within this range in the correspondent condition" (Rauchbauer, Majdandžić, Hummer, Windischberger, & Lamm, 2015, p. 54).

For T1, two 3x2 (condition x group) mixed-model ANOVAs were conducted for early and late SPN mean amplitudes separately with the within-subjects factor *condition* (CNP, CP, UC) and the between-subjects factor *group* (HC, MDD). For the statistical analysis of T2 a subsample had to be drawn, because not all MDD patients underwent the second measurement. Hence, the MDD sample for the analysis of T2 consisted of those 19 MDD patients who took part in the pre- and after-treatment EEG measurement. From the HC sample a random subsample comprising 19 individuals was drawn to equal sample sizes for T2. Subsequently, two separate 3x2x2 (condition x group x time) mixed-model ANOVAs were conducted using early and late SPN mean amplitudes from the subsample including T1 and T2. Within-subjects factors were *condition* (CNP, CP, UC) and *time* (T1, T2), whereas *group* (HC, MDD) represented the between-subjects factor. In order to evaluate the direction of significant effects, within-subjects contrasts were calculated, for which the UC condition served as reference category

In cases of violation of the assumption of sphericity, Greenhouse-Geisser estimates of sphericity were used to correct the degrees of freedom.

In the case of significant effects, partial-eta squared (ηp^2) was calculated for effect sizes, where 0.01, 0.06 and 0.14 represent small, medium and large effects (Kirk, 1996).
The significance level was set to $p < 0.05$.

3.2 Behavioral data

Regarding the analysis of the behavioral data, absolute lower and upper pain thresholds were compared in both groups (HC, MDD) and measurements (T1, T2) using Wilcoxon signed-rank tests. Subsequently, differences between upper and lower thresholds were calculated to assess relative differences in pain thresholds. Mann-Whitney tests were carried out to compare relative thresholds between groups. Further Wilcoxon-signed rank tests were used to compare relative pain thresholds between measurements. Pearson's correlation coefficients were used as effect sizes for significant results, with values of $r = 0.1$, 0.3 and 0.5 reflecting small, medium and large effects (Cohen, 1992). The significance level was set to $p < 0.05$.

3.3 Questionnaire data

In order to compare relevant personality dimensions between groups, Mann-Whitney tests were carried out for the questionnaire data in the HC and MDD group, including PCS, LOT-R and UGTS scores. Further, Wilcoxon signed-rank tests for HAM-D and BDI scores at T1 and T2 were performed to assess the change in depressive symptoms in the MDD group from before and after treatment. For both non-parametric measures Pearson's correlation coefficients were calculated for effect sizes, with values of $r = 0.1$, 0.3 and 0.5 reflecting small, medium and large effects (Cohen, 1992). To assess the relationship between relevant personality dimensions and anticipatory EEG activity, Spearman correlations for questionnaire scores and SPN mean amplitudes in T1 were conducted. This analysis was carried out for SPN amplitudes in T1 only, because the questionnaire scores were assessed only once preceding T1. Values of $r = 0.1$, 0.3 and 0.5 reflect small, medium and large relationships (Cohen, 1992). In order to assess the differences of the correlation coefficients

between the groups, Steiger's z-tests were carried out, following Fisher's z-transformations. The significance level was set to $p < 0.05$.

4 Results

4.1 ERP data

For the following description of ERP results is important to note that numerically smaller values of SPN mean amplitudes reflect a stronger expression of the SPN component, which in turn represents more pronounced anticipatory responses. Conversely, numerically larger values of SPN mean amplitudes reflect an attenuated SPN component and hence less pronounced anticipatory responses. In the following, SPN mean amplitudes will be referred to as SPN amplitudes for reasons of simplification.

4.1.1 Early anticipation

The ANOVA for early SPN amplitudes in T1 did not reveal significant main effects for the factors condition ($F(2,120) = 1.58$, $p = .209$) and group ($F(1,60) = .69$, $p = .411$). The interaction condition x group ($F(2,120) = .38$, $p = .686$) did not reach significance either. As indicated in Table 1 however, SPN amplitudes were descriptively more negative for MDD compared to HC across all conditions. The difference between groups was largest for the UC condition. Whereas the UC condition elicited most negative SPN amplitudes followed by CP and CNP in MDD, SPN amplitudes were more negative for CP than UC and CNP in the HC group. See Figures A1 and A2 for a depiction of early SPN mean amplitudes for T1.

Table 1: *Descriptive Statistics of early SPN (in µV) in Time 1 (group, mean, standard deviation)*

	Group	**Mean**	**SD**
Certain No Pain	HC	0.92	1.96
	MDD	0.73	2.58
Certain Pain	HC	0.48	2.17
	MDD	0.28	2.13
Uncertain	HC	0.64	1.70
	MDD	-0.04	2.60

Results of the second ANOVA for early SPN amplitudes with the subsample data including T1 and T2 revealed a significant main effect for condition ($F(2,72) = 3.75$, $p = .028$, $\eta p^2 = .094$). Contrasts revealed that SPN amplitudes were significantly smaller for CNP compared to UC ($F(1,36) = 6.83$, $p = .013$, $\eta p^2 = .159$). The contrast comparing CP to UC ($F(1,36) = .94$, $p = .338$) did not reach significance. Further, a significant main effect for time ($F(1,36) = 5.19$, $p = .029$, $\eta p^2 = .126$) revealed smaller SPN amplitudes for T1 compared to T2. Neither a significant main effect for group ($F(1,36) = .28$, $p = .598$), nor significant interaction effects could be observed: condition x group ($F(2,72) = 1.51$, $p = .228$), time x group ($F(1,36) = .01$, $p = .923$), condition x time ($F(2,72) = .14$, $p = .872$), and condition x group x time ($F(2,72) = 1.54$, $p = .220$).

Table 2 gives an overview of SPN mean values per condition, group and time. When taking into account the descriptive statistics of the early SPN component, the following observations can be made: in T1, SPN amplitudes were more negative in the MDD group compared to HCs across all conditions. While this difference was only barely noticeable in the CNP condition, it was slightly larger in UC and most pronounced in the CP condition, which stands in contrast with findings including the whole sample, where the difference between groups was largest in the UC condition. Considering the whole HC sample, most negative SPN amplitudes were observed in CP, while the analysis of the descriptive statistics of subsample revealed most negative amplitudes in UC. Similarly, the most negative SPN amplitudes were elicited by the UC condition in the MDD subsample.

Regarding T2, SPN amplitudes were more pronounced for CNP, but less negative in CP and UC in the HC compared to the MDD group. Within the HCs, CP evoked most negative SPN amplitudes, followed by CNP and CP. Comparing T1 and T2 in HC revealed considerably more pronounced SPN amplitudes in CNP and CP conditions i T2, while SPN amplitudes stay similar in UC across measurements. In the MDD group UC elicited most negative SPN amplitudes, followed by CP and CNP. Although the course of SPN amplitudes stays similar across measurements in MDD, T2 is characterized by substantially more negative SPN amplitudes. See Figures A3 and A4 for a depiction of early SPN mean amplitudes for T2.

Table 2: *Descriptive Statistics of early SPN (in µV) with subsample (group, time, mean, standard deviation)*

	Group	Time	Mean	SD
Certain No Pain	HC	1	1.00	2.11
		2	0.15	1.79
	MDD	1	0.98	3.11
		2	0.72	2.45
Certain Pain	HC	1	0.89	2.42
		2	-0.19	1.88
	MDD	1	0.28	2.25
		2	-0.24	2.35
Uncertain	HC	1	0.21	1.85
		2	0.36	2.37
	MDD	1	0.10	2.41
		2	-1.06	2.96

4.1.2 Late anticipation

Regarding the late SPN component in T1, a significant main effect for condition was observed ($F(2,120) = 4.78$, $p = .01$, $\eta p^2 = .074$). As indicated by contrasts, the significant difference between the CNP and UC condition ($F(1,60) = 12.12$, $p = .001$, $\eta p^2 = .168$) accounts for this effect with UC eliciting more negative SPN amplitudes. The contrast comparing CP and UC ($F(1,60) = 1.48$, $p = .228$) did not reach significance. Further, a main effect for group on a trend level was found ($F(1,60) = 3.55$, $p = .064$, $\eta p^2 = .056$), suggesting more negative SPN amplitudes in the MDD group compared to HCs. The data did not yield a significant interaction effect for condition x group ($F(2,120) = .41$, $p = .661$). Table 3 illustrates descriptive statistics of the late SPN component, which show that SPN amplitudes were more negative in MDD compared to HC across all conditions. In both groups the UC condition elicited most negative SPN amplitudes, followed by CP and CNP. See Figures A5 and A6 for a depiction of late SPN mean amplitudes for T1.

Table 3: *Descriptive Statistics of late SPN (in µV) in Time 1 (group, mean, standard deviation)*

	Group	Mean	SD
Certain No Pain	HC	-0.48	2.12
	MDD	-1.83	2.51
Certain Pain	HC	-1.62	2.26
	MDD	-2.24	3.77
Uncertain	HC	-2.17	2.38
	MDD	-2.87	3.05

Results of the second ANOVA for late SPN amplitudes with the subsample data including T1 and T2 revealed a significant main effect for condition ($F(2,72) = 4.08$, $p = .021$, $\eta p^2 = .102$). Contrasts revealed a significant difference between the CNP and UC condition ($F(1,36) = 9.37$, $p = .004$, $\eta p^2 = .206$) only, with smaller SPN amplitudes in CNP compared to UC. The contrast comparing CP to UC ($F(1,36) = 1.47$, $p = .234$) revealed that SPN amplitudes between the CP and UC condition did not differ significantly. Main effects of group ($F(1,36) = 1.48$, $p = .231$) and time ($F(2,36) = .23$, $p = .635$), as well as corresponding interaction effects of condition x group ($F(2,72) = .08$, $p = .922$), time x group ($F(1,36) = .002$, $p = .965$) and condition x time x group ($F(2,72) = .78$, $p = .463$) did not yield significant results.

Table 4 gives an overview of descriptive statistics of late SPN data in the subsample. In T1, late SPN amplitudes were more pronounced in MDD compared to HC across all conditions with most negative SPN amplitudes for the UC condition, followed by CP and CNP. This difference between groups was found to be largest in the CNP condition, which is in line with findings from the whole sample. Similarly, the MDD group elicited more pronounced SPN amplitudes than the HC group across conditions in T2. Here, this difference was largest for CP. Within the HC group, SPN amplitudes remained closely the same across measurements in CP, while amplitudes for CNP increased and amplitudes observed for UC decreased from T1 to T2. In the MDD group, the UC condition elicited similar SPN amplitudes across time, whereas CNP and CP evoked more pronounced SPN amplitudes in T2. See Figures A7 and A8 for a depiction of late SPN mean amplitudes for T2.

Table 4: *Descriptive Statistics of late SPN (in µV) with subsample (group, time, mean, standard deviation)*

	Group	Time	Mean	SD
Certain No Pain	HC	1	-0.47	2.19
		2	-1.71	2.25
	MDD	1	-1.85	2.85
		2	-2.05	3.09
Certain Pain	HC	1	-1.84	2.73
		2	-1.87	2.41
	MDD	1	-2.23	4.32
		2	-2.76	2.90
Uncertain	HC	1	-2.78	2.48
		2	-2.09	1.79
	MDD	1	-3.09	3.13
		2	-2.84	2.90

4.2 Behavioral data

The Wilcoxon signed-rank test applied on absolute pain thresholds revealed that lower thresholds (Mdn_{T1} = 1.0, Mdn_{T2} = 1.0) differed significantly from upper thresholds (Mdn_{T1} = 3.5, Mdn_{T2} = 3.0) among HCs in T1, z = 4.86, p < .001, r = .87 and T2, z = 4.86, p < .001, r = .87. In the MDD group, significant differences between absolute lower (Mdn_{T1} = 1.3, Mdn_{T2} = 1.25) and upper threshold (Mdn_{T1} = 3.85, Mdn_{T2} = 4.25) were found for T1, z = 4.86, p < .001, r = .87 and T2, z = 3.92, p < .001, r = .88 as well.

Mann-Whitney tests for relative pain thresholds found that thresholds did not differ between the HC (Mdn_{T1} = 2.6, Mdn_{T2} = 2.3) and MDD group (Mdn_{T1}= 2.25, Mdn_{T2} = 3.0) in T1, U = 496, z = .22, p = .82 and T2, U = 323.50, z = .58, p = .56.

Wilcoxon signed-rank tests for the HC group showed that thresholds inT1 (Mdn= 2.6) did not differ significantly from thresholds at T2 (Mdn = 2.3), z = .18, p = .86. In the MDD group, pain thresholds in T1 (Mdn = 2.25) did not differ significantly from those at T2 (Mdn = 3.0) either, z = -.020, p = .98.

4.3 Questionnaire data

4.3.1 Personality dimensions

Results from the Mann-Whitney tests for PCS scores revealed significantly higher levels of pain catastrophizing for MDD (*Mdn* = 2.69) compared to HC (*Mdn* = 2.08), $U = 680.50$, $z = 2.82$, $p = .005$, $r = .35$.

Regarding the LOT-R, significantly higher optimism scores were found for HC (*Mdn* = 3.33) compared to MDD (*Mdn* = 1.83), $U = 50.50$, $z = -6.07$, $p < .001$, $r = -.77$.
Tolerance of uncertainty, as assessed by UGTS scores, was shown to be significantly higher in HC (*Mdn* = 3.88) than in MDD (*Mdn* = 3.38), $U = 337$, $z = -2.03$, $p = .043$, $r = -.25$.

The Wilcoxon signed-rank tests performed with before- and after-treatment HAM-D and BDI scores showed that depressive symptoms reduced significantly from T1 (Mdn = 28.0) to T2 (*Mdn* = 5.0), $z = -3.83$, $p < .001$, $r = -.88$ for the HAM-D. Similarly, BDI scores were significantly reduced after treatment in T2 (*Mdn* = 4.0) compared to baseline scores in T1 (*Mdn* = 22.0), $z = -3.79$, $p < .001$, $r = -.87$

4.3.2 Correlation analyses

Significant Spearman correlations were mostly found for pain catastrophizing scores and more often in the MDD group. During early anticipation, a significant relationship between the SPN amplitude in CNP and PCS scores was found in MDD. For the HC group a strong negative relationship was observed for PCS scores in CP, whereas this relationship was moderate and positive in MDD. The comparison of these correlation coefficients revealed that correlations differed significantly ($p < .001$) between the groups, underlining the contrary relationship between pain catastrophizing and early anticipation of CP found in the HC and MDD group.

Regarding late SPN amplitudes, moderate positive relationships were found for PCS scores in CNP and CP in the MDD group. Further, a moderate negative relationship between LOT-R scores and SPN amplitudes in the UC condition in the HC as well as MDD group was found. Table 6 gives an overview of significant correlations and group differences regarding correlation coefficients.

Table 6: *Group differences (p) and correlation coefficients (Spearman's rho) of SPN mean amplitudes (in µV) in Time 1 with questionnaire scores per condition (CNP, CP, UC)*

	Condition	Questionnaire	r_{HC}	r_{MDD}	$p_{(two\text{-}tailed)}$
Early SPN	CNP	PCS	-.103	**.371***	.06
	CP	PCS	**-.559****	**.386***	**<.001**
Late SPN	CNP	PCS	-.045	**.479****	**.03**
	CP	PCS	.078	**.364***	.25
	UC	LOT-R	**-.378***	**-.371***	.98

* Correlation is significant at the level of 0.05 (2-tailed)

** Correlation is significant at the level of 0.01 (2-tailed)

Significant results are printed in bold.

5 Discussion

The present thesis investigated the influence of uncertainty on pain anticipation in healthy individuals and patients with MDD before and after treatment with antidepressant medication. While EEG was recorded, participants underwent an anticipation paradigm based on visually presented cues, in which painful or non-painful stimulation was delivered with certainty or uncertainty following the anticipation cue. In the following section, the obtained results will be discussed.

5.1 ERP data

The discussion of the ERP data for early SPN amplitudes is based on the results of the ANOVA including T1 and T2. The data firstly revealed that uncertain trials elicited most pronounced SPN amplitudes during early anticipation. This effect was observed across groups and time, indicating a predominant influence of uncertainty on pain anticipation processes independent from psychopathology. We expected uncertainty to be associated with stronger early anticipation for both, healthy and depressive individuals, since early anticipation is said to reflect basic attentional orienting processes and rather be linked to affective components of anticipation. Hence, these early anticipation processes were thought to be enhanced by uncertainty, since uncertain situations are perceived as more threatening and increase anxiety (Lin, Hsieh, Yeh, & Niddam, 2014). Anxiety in turn is mediated by attentional processes, because it raises attention allocation towards the threatening stimulus (Grillon, Baas, Cornwell, & Johnson, 2006; Vansteenwegen, Iberico, Vervliet, Marescau, & Hermans, 2008).

Secondly, early SPN amplitudes were found to be more pronounced in the second measurement across conditions and groups. Although SPN amplitudes were rather expected to remain stable across measurements in both groups, the so-called emotion context insensitivity hypothesis (Rottenberg & Gotlib, 2004) might provide an explanation for enhanced anticipation of pain in MDD patients after antidepressant medication. According to the emotion context insensitivity hypothesis, depressed mood impairs variation in emotional responses to stimuli of positive and negative valence, which is moderated by the severity of depressive symptoms, i.e. stronger inhibition of emotional responses linked to a more severe depressive symptomatology. Given that depressive symptoms of MDD patients were significantly reduced after treatment in our study, stronger anticipation to emotionally salient

painful or non-painful stimuli in the second measurement seems plausible. Generally, the greater extent of early anticipation processes after treatment of MDD indicates a lack of influence of antidepressant medication on early phases of pain anticipation. This is in line with evidence indicating that antidepressant drugs act on depressive and pain symptoms independently (Arnold et al., 2005).

This does not however take into account the time effect for healthy individuals.. The significant difference in SPN amplitudes between measurements suggests the SPN to be variable over time, and hence opposes the expected stability of the SPN component. Stability of the SPN component over time was assumed due to similarities of CNV with SPN amplitudes (Brown, 2017) and findings of stable CNV amplitudes over a period of 10 days (Kropp et al., 2000). However, stability over a period of 10 days might not be comparable to the period of 12 weeks that separated both measurements in the present study. Nevertheless, a distinct interpretation of the observed effect of time on early SPN amplitudes for each group remains critical, because the effect was found across groups. Hence, the effect might be specific to the early SPN component rather than to the HC and MDD group.

For late anticipation, ERP data revealed an effect of uncertainty across groups and time, which was found in both ANOVA models, i.e. the model including T1 data and the model including T1 as well as T2 data. This resembles the effect found in early anticipation, i.e. most pronounced SPN amplitudes during uncertain trials. This finding is rather surprising, since processes of late anticipation were assumed to be strongest for certain pain trials in HCs, because certainty regarding an upcoming stimulus was said to most prominently engage immediate preparatory mechanisms (Seidel et al., 2015). However, an fMRI study in which participants anticipated highly potent aversive and positive video clips revealed all regions selectively active during negative and positive anticipation to be active during uncertain anticipation (Greenberg, Carlson, Rubin, Cha, & Mujica-Parodi, 2015). This suggests uncertain anticipation to represent a preparatory response to both positive and negative stimuli, which might account for the observed enhanced late SPN amplitudes during uncertain pain anticipation. Further support for strongest late anticipatory processes observed during uncertainty comes from Brown et al. (2008), who found fronto-parietal networks to be more active during uncertain compared to certain pain anticipation. The authors propose these networks to be recruited for purposes of cognitive control, such as conditions of uncertainty. Despite an association of the late SPN component with centro-parietal rather than fronto-parietal activations, the observed need for cognitive control during uncertain anticipation

might be in line with enhanced late anticipation in uncertain trials, since late anticipation was said to rather reflect cognitive anticipation and preparatory activity.

As mentioned before, the SPN component closely resembles the CNV component in some aspects (Brown, 2017), such as the separation in early and late anticipation phases, which for the CNV component are termed initial and terminal CNV (Birbaumer, Elbert, Canavan, & Rockstroh, 1990). Given that unlike initial CNV amplitudes, terminal CNV amplitudes increase with uncertainty over the upcoming imperative stimulus compared to a certainly determined response (Lütcke, Gevensleben, Albrecht, & Frahm, 2009; van Boxtel & Brunia, 1994), our findings of strongest late SPN amplitudes during uncertain pain anticipation appear plausible.

All in all, uncertainty during pain anticipation seems to require stronger engagement of cognitive control and preparatory mechanisms than anticipating certain pain. While these results contradict our original hypothesis of enhanced late anticipatory processes for certain pain in HCs, findings in the MDD group contradict the expected outcomes as well. For depressive individuals, the enhanced late anticipation of certain pain was proposed to be attenuated due to dysfunctional top-down modulatory mechanisms. Unexpectedly, a close to significant group effect found in the ANOVA model for T1 data, revealed overall late SPN amplitudes to be more pronounced in MDD patients compared to HCs. This suggests MDD to be linked to a stronger need for mechanisms of cognitive control and stimulus preparation during the anticipation of certainly or uncertainly aversive and neutral stimuli. When performing an effortful cognitive task, hyperactivity in the dorsal ACC and the lateral PFC has been observed in depressed individuals (Harvey et al., 2005). These regions have been associated with complementary cognitive functions such as an executive component regulated by the DLPFC and an attentional processing system regulated by the ACC (Braver et al., 1997; Carter et al., 1998). These findings indicate that depressive individuals require more brain activation in the processing regions to reach normal functioning during cognitive effortful tasks. Despite the fact that the pain anticipation paradigm used in the current study cannot be regarded a cognitive effortful task, findings of increased dorsal ACC activity during the anticipation of heat pain (Strigo et al., 2008) and the association of dorsal ACC hyperactivity with increased cognitive control in MDD (Harvey et al., 2005), might support our observations of higher levels of cognitive control needed for the anticipation of possibly or certainly painful or non-painful stimuli in depressive individuals.

Next, the absence of an effect of time in late anticipation corresponds with our hypothesis of unchanged pain anticipation after administration of antidepressant drugs in

MDD. Despite an amount of evidence indicating normalization of abnormal anticipation processes in MDD after treatment with antidepressant medication (Stoy et al., 2012; Vanderhasselt et al., 2012), late anticipatory responses to pain did not differ before and after treatment in MDD. This might be due to a lack of influence of antidepressant drugs on cognitive domains involved in late phases of anticipation. According to Rosenblat et al. (2016), antidepressant drugs do not affect cognitive control in patients with MDD, which plays a major role in late anticipation processes. Moreover, a study with geriatric patients undergoing antidepressant treatment with SSRIs revealed that cognitive dysfunction persisted after treatment despite an improvement of the patients' mood disorder (Nebes et al., 2003). Further support comes from measurements of cerebral blood flow, suggesting that SSRIs primarily act on affective instead of cognitive components of pain (Graff-Guerrero et al., 2008). Besides, various MDD samples, including acute, medicated and remitted patients have repeatedly been associated with reduced gray matter volume in the insula, suggesting alterations in the insula to represent a trait-characteristic of depression (Jung et al., 2014, Liu et al., 2014). Due to the fact that the insula represents one of the main sources of the SPN component, the maintenance of SPN amplitudes after treatment in MDD might evolve from persisting insular alterations. As in early anticipation, time effects in the healthy group give an indication of the stability of the SPN component. Whereas a change in time of SPN amplitudes was found in early anticipation, a first hint for stability of the SPN component over a period of 12 weeks was found for late anticipation. This suggests the early and late SPN component to differ regarding their stability over time. However, an analysis of reliability would be necessary to infer stability of the SPN component.

Apart from the previously discussed results obtained from the ERP data, one main hypothesis of this thesis could not be corroborated by the current data. For early as well as late pain anticipation the HC and MDD group were expected to differ from each other. However, apart from the trend level group effect for late anticipation mentioned before, no significant differences between the groups could be found. In the following, possible explanations for this lack of differences will be presented.

Firstly, although hypothesized, patients with MDD might not anticipate pain abnormally. Evidence from a paradigm assessing the blink magnitude during emotional picture anticipation did not find differences between participants with symptoms of depression and those that were never-depressed, indicating an intact ability to anticipate stimuli of positive or negative valence in individuals with depressive symptoms (Moran, Mehta, & Kring, 2012). However, this study might not provide adequate support for our

findings, since anticipatory processes were only captured on a behavioral level, the anticipated stimuli consisted of emotional pictures and the sample was not clinical.

The possible explanations presented secondly, rather take cognitive and attentional biases into consideration that were proposed to account for abnormal anticipation processes in depression. A study assessing future-directed thinking in depressive and healthy individuals did not find a cognitive bias towards negative future events in the depressive group (Bjärehed, Sarkohi, & Andersson, 2010). Further, studies investigating unconscious stimulus processing have revealed that MDD patients are not subject to an attentional bias towards depression-relevant masked stimuli. When applying an emotional stroop task in a depressive sample, reactions to subliminally presented negative words were not different from those of HCs (Lim & Kim, 2005; Mogg, Bradley, & Mathews, 1993). According to a review from Teachman, Joormann, Steinman, & Gotlib (2012) on automaticity in MDD, most features that comprise automatic processing have not been shown to be altered in depression, suggesting that automatic processing does not play a central role in MDD and underlining the evidence from unconscious processing in MDD. Given that early anticipatory responses to pain were proposed to be enlarged due to attentional biases in the form of enhanced attention allocation toward negative upcoming stimuli in MDD, the previously presented lack of altered unconscious processing in MDD might support our null findings in anticipation between HCs and MDD. Regarding early anticipation, it can further be argued that deficits in attention associated with depression (Beck, 1964) might play a role in the absence of enhanced anticipation of pain expected in MDD, since attending to pain leads to higher pain perception, which is mediated by anticipation processes (Arntz & de Jong, 1993).

In healthy individuals, attention to an upcoming pain stimulus as well as negative emotions, for instance elicited by uncertainty, are supposed to enhance anticipatory responses to pain. Whereas individuals with MDD are even more likely to experience negative affect in anticipation of a negative event, which should result in stronger pain anticipation, the absence of enhanced attentional allocation towards upcoming negative events found in depressive samples possibly due to deficits in attention (see Joormann & Quinn, 2014) might in turn impair pain anticipation processes. Due to difficulties in separating attentional and emotional pain modulation (Roy, 2015), the observed lack of differences between healthy and depressive individuals regarding pain anticipation might hence be a result of neutralization of possible effects found in the MDD group. In order to further elucidate the influence of attentional processes on anticipatory responses to pain, future research should focus on earlier ERP components preceding the SPN component.

Taken together, attentional and cognitive biases that were assumed to occur in depression and to modulate anticipatory processing could not be found in MDD patients in previous research, providing support for the intact pain anticipation observed in our MDD sample. However, there is no evidence for a clear link between these biases and the neurophysiological manifestation of pain anticipation. Still, it can be argued that for instance early stage attentional biases, rather affect ERPs that capture temporally early processes than acting on haemodynamic responses measured via fMRI. The fact that depressed individuals are indeed characterized by attentional biases in later processing stages (Donaldson, Lam, & Mathews, 2007), provides support for abnormal neural activity during pain anticipation in depression (Strigo et al., 2008; Strigo et al., 2013), as measured via fMRI activation patterns that reflect more elaborate neural activity.

Apart from these possible interpretations specific to anticipation processes, a more general factor should be considered to account for the obtained results. Depression has convergingly been identified as heterogeneous disorder. Specifically, it was suggested to subdivide depression into melancholic and non-melancholic depression, because both subtypes were found to differ in terms of cognitive dysfunction (Parker, 2000; Zaninotto et al., 2016). In a study investigating ERPs related to inhibitory control, subtypes of depression affected behavioral (but not ERP) outcomes and melancholic depression was linked to psychomotor disturbance and symptom severity (Quinn, Harris, & Kemp, 2012). Given that the current study assessed depressive symptoms in the patient sample, but did not take into account other characteristics that could identify subtypes of the disorder, it surges that neglecting the heterogeneity of depression might add to the absence of differences between the HC and MDD group. Especially a separation into groups differing in severity of depressive symptoms would have been advantageous, since the degree of depressive symptomatology has been linked to dysfunctional anticipation processes (Stoy et al., 2012). However, sample sizes were too small to allow a subdivision into groups of depressive subtypes or symptomatology.

5.2 Behavioral data

Firstly, analysis of the behavioral data revealed that pain thresholds did not differ between healthy and depressive individuals neither in the first nor the second measurement. This indicates that the current depressive patients perceived pain in a similar manner as the current

healthy controls. Despite an expected difference regarding pain thresholds between the MDD and HC group, research to date could not consistently find altered pain thresholds in MDD. Generally, these inconsistencies might be explained by the underlying modalities of painful stimulation. Whereas superficial pain, such as painful electrical stimulation has been associated with enhanced thresholds in MDD, thresholds for "deep somatic" pain have been shown to be attenuated in patients with MDD (Thompson et al., 2016). Next to pain modality, duration and lateralization of painful stimulation might impact perception outcomes. Regarding duration, longer lasting painful stimulation was found to be linked to higher levels of arousal compared to phasic pain (Sinke, Schmidt, Forkmann, & Bingel, 2015), suggesting that the short duration of painful stimulation applied in the present study might account for the lack of threshold differences between the groups. A possible explanation for decreased sensitivity to brief experimental pain found earlier in MDD might lie in a true sensory deficit, slower reaction times or affective indifference in depression (Piñerua-Shuhaibar et al., 1999). Further, thermal and electrical pain thresholds were found to be increased on the right side of the body in patients with MDD (Bär et al., 2005; Schwier et al., 2010), suggesting an effect of lateralization on pain perception in depression. Therefore, the fact that painful stimulation was applied to the left side of the body in the current study, might add to the lack of differences between the HC and MDD group, because electrical stimulation to the left body side might compensate for typically increased electrical pain thresholds observed in MDD. Taken together, there are several factors that modulate pain perception in MDD and hence might account for the obtained results.

Secondly, the behavioral data showed that pain thresholds did not differ between measurements in MDD patients, indicating that antidepressant medication did not impact pain perception. As will be discussed in the following section, depressive symptoms decreased significantly after treatment in the present study. Given the maintenance of pain thresholds across time in the MDD group, this contradiction between pain thresholds and depressive symptomatology provides support for the notion of an independent influence of antidepressant drugs on depressive versus pain symptoms (Arnold et al., 2005).

In the control group, pain thresholds did not differ between measurements either, which points to a stability of pain perception across time in healthy individuals.

5.3 Questionnaire data

On the one hand, data from the questionnaires capturing pain- and depression-relevant personality dimensions revealed that depressive patients catastrophize pain to a greater extent than healthy individuals. This is in line with evidence for a positive association between pain catastrophizing and depression (Quartana et al., 2009).

However, these outcomes are not consistent with our ERP data, which could not find pain anticipation in MDD to differ from that in HCs. The correlation analyses between questionnaire scores and SPN amplitudes found pain catastrophizing to be strongly linked to enhanced early SPN amplitudes during certain pain in HCs, whereas this relationship was positive in the MDD group. Given that the reported correlations represent rather parallel processing, the contrasting results between the groups indicate that while healthy individuals who stronger catastrophize pain, also anticipate pain to a stronger extent, depressive patients who show higher levels of pain catastrophizing, anticipate pain to a lesser extent on a neurophysiological basis. For late SPN amplitudes a similar association between attenuated anticipatory responses to certain pain and no-pain and stronger catastrophizing of pain was observed in the MDD but not the HC group. In line with the behavioral data indicating pain thresholds in MDD patients to resemble those in HCs, these findings suggest that although depressive individuals evaluate pain differently on a cognitive basis, these differences do not manifest themselves on a physiological or neurophysiological basis.

On the other hand, questionnaire data revealed MDD patients to score lower on optimism and on tolerance of uncertainty compared to HCs, which supports the findings of previous research (e.g. Achat, Kawachi, Spiro, DeMolles, & Sparrow, 2000).

With respect to optimism, the correlation analysis revealed optimism scores to be associated with stronger late anticipatory responses to uncertain pain in HCs and MDD. Given that late anticipation is involved in preparatory activity, higher optimism towards an uncertain situation might hence result in stronger preparation to a possibly negative upcoming stimulus. Regarding tolerance of uncertainty, the reduced scores observed in the MDD group correspond with IU as vulnerable factor for MDD (Yook et al., 2010). Besides, the observed enhanced anticipatory response during uncertain trials supports the association of IU with depression.

Next, the scales capturing depressive symptomatology showed that depressive symptoms were significantly reduced after antidepressant treatment in the MDD group. Whereas cutoff values of mean baseline BDI and HAMD scores showed that the depressive sample presented

symptoms of a moderate depression, after-treatment cutoffs fell below the criterion for a depressive disorder. This suggests a positive effect of antidepressant medication on depressive symptoms.

5.4 Limitations

The present study is subject to a range of limitations, which are mainly methodological in nature. Firstly, the unequal number of participants in the two measurements might restrict our results. Due to dropouts of participants throughout the 12 weeks in between both measurements, the sample size for T1 and T2 were not equal. Although data of T1 and T2 was analyzed in separate statistical models to account for this inequality, a comparison of results from the whole sample and the subsample proved itself difficult, because findings from the whole sample could not be replicated accurately in the subsample. This points to an unrepresentative subsample. Still, the results remained similar for a variety of random subsamples that were drawn.

Secondly, sample sizes were too small to subdivide the MDD group into subgroups according to severity of depressive symptoms or other characteristics that define subtypes of the disorder. Given that depression was identified as heterogeneous disorder and that symptom severity has been shown to mediate abnormal neural activations during anticipation (Stoy et al., 2012), a division of the MDD group into subgroups might have been beneficial, or alternatively, a dimensional approach integrating symptom severity into the statistical models.

Thirdly, there are some considerations about the anticipation paradigm applied in the present study. First of all, the pain anticipation paradigm comprised relatively few trials. According to a pilot study by Seidel and colleagues (2015) this small number was sufficient to obtain consistent results. However, as some trials had to be eliminated during preprocessing due to artifacts in the EEG data, a larger number of trials, especially for the uncertain condition would possibly improve the reliability of our findings. Next, applying electrical stimulation to evoke pain might restrict our results, because longer-lasting pain transmitted via unmyelinated C-fibers has rather been associated with lasting pain symptoms in MDD than superficial pain transmitted via A-delta fibers (Bear, Connors, & Paradiso, 2007). Hence, future studies could apply different pain modalities that lead to longer-lasting pain sensations. Moreover, the paradigm did not include ratings of the perceived pain

intensity in order to capture rather automatic neural processes unaffected by cognitive processes. Still, a behavioral measure of subjective stimulus intensity may have provided important information regarding the observed contradiction between cognitive and neural measures of pain anticipation. Last, painful stimulation occurred within a variable time window during the anticipation phase in order to induce uncertainty regarding the stimulus timing and hence avoid adaptation mechanisms. However, uncertainty regarding stimulus timing was found to affect pain-related ERPs, while greater anticipation duration was found to increase pain perception (Clark, Brown, Jones, & El-Deredy, 2008). This indicates that uncertainty regarding stimulation onset may confound our ERP results.

6 Conclusion

The present thesis was the first EEG study to investigate pain anticipation in acutely depressed patients before and after antidepressant treatment and to compare anticipation-related ERPs to those of healthy individuals assessed at two time points. This represents a promising approach for studying treatment effects of antidepressant medication on pain-related processes and for unraveling putative trait-markers for depression, which might indicate vulnerability to the illness. The study further emphasized the role of uncertainty during pain anticipation, adding important knowledge to the research on anticipation processes and leading to a better understanding of the neurophysiological manifestation of depressive disorders.

Breaking down the obtained results, the present study led to two main insights. On the one hand, uncertainty during pain anticipation evoked enhanced anticipatory responses, irrelevant of psychopathology and the mechanisms active during anticipation. This points to a superior role of uncertainty during the anticipation of upcoming events. On the other hand, in patients with MDD, pain-related cognitive evaluations were not consistent with physiological and neurophysiological outcomes. Whereas depressive patients exhibited higher pain catastrophizing and intolerance of uncertainty than healthy individuals according to self-report measures, pain thresholds and neurophysiological measures of pain anticipation did not differ from HCs significantly This alteration of cognitive aspects of the pain experience in MDD paired with the lack of a neurophysiological manifestation of such alterations might point to a maladaptive mechanism in depression. Such a maladaptive mechanism could possibly account for a cognitive bias in depression that implies evaluating negative events as more aversive.

However, the limitations of the present study have to be considered a possible cause for the unexpected lack of ERP differences between patient and control group. The limitations can further act as starting point for future research, which could apply a modified anticipation paradigm, a different pain modality, and taking severity of depressive symptoms into account.

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List of Abbreviations

ACC	anterior cingulate cortex
BDI	Beck Depression Inventory
CNP	certain no-pain
CNV	contingent negative variation
CP	certain pain
EEG	electroencephalography
ERP	event-related potential
fMRI	functional magnetic resonance imaging
HAM-D	Hamilton Depression Scale
HC	healthy control subject
IU	intolerance of uncertainty
LOT-R	Life Orientation Test Revised
MDD	major depressive disorder
PCS	Pain Catastrophizing Scale
PFC	prefrontal cortex
rMDD	remitted major depressive disorder
S1	primary somatosensory cortex
S2	secondary somatosensory cortex
T1	time 1
T2	time 2
SPN	stimulus-preceding negativity
SSRI	selective serotonin reuptake inhibitor
UC	uncertain pain
UGTS	Ungewissheitstoleranzskala

Appendix

Figure A1

Early SPN mean amplitudes at FCz and surrounding electrode sites for conditions CNP, CP and UC in the HC group at T1.

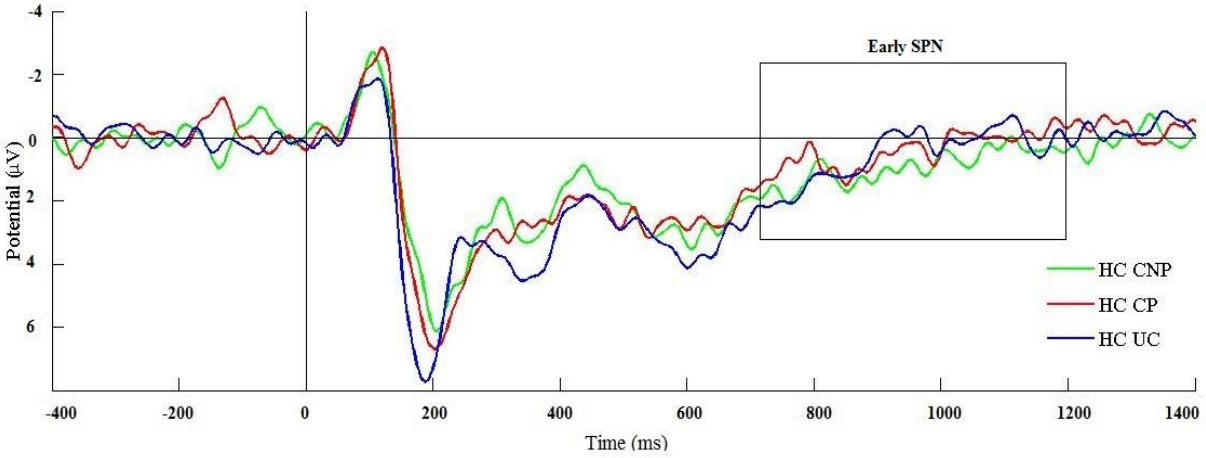

Figure A2

Early SPN mean amplitudes at FCz and surrounding electrode sites for conditions CNP, CP and UC in the MDD group at T1.

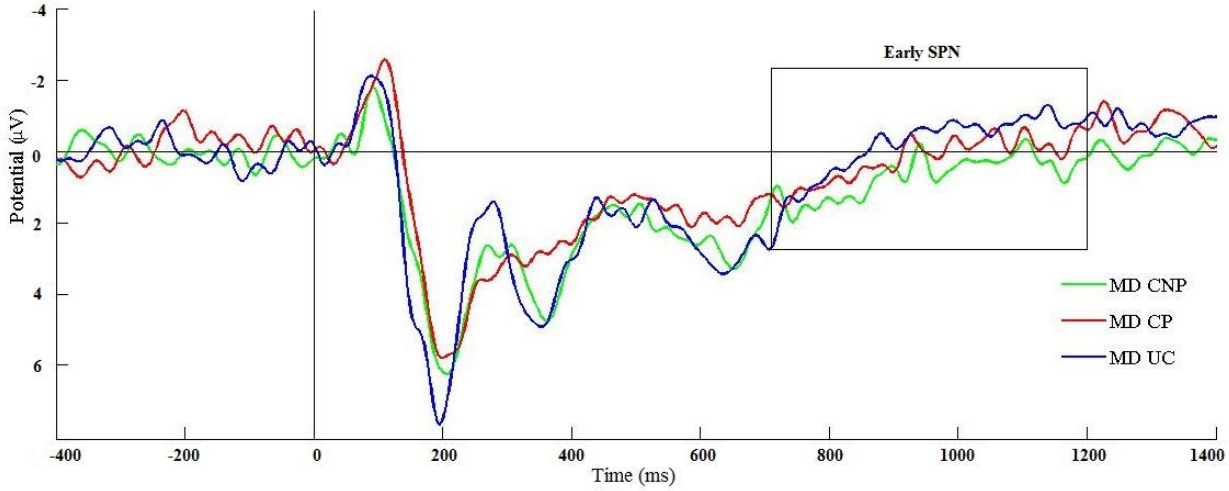

Figure A3

Early SPN mean amplitudes at FCz and surrounding electrode sites for conditions CNP, CP and UC in the HC group at T2.

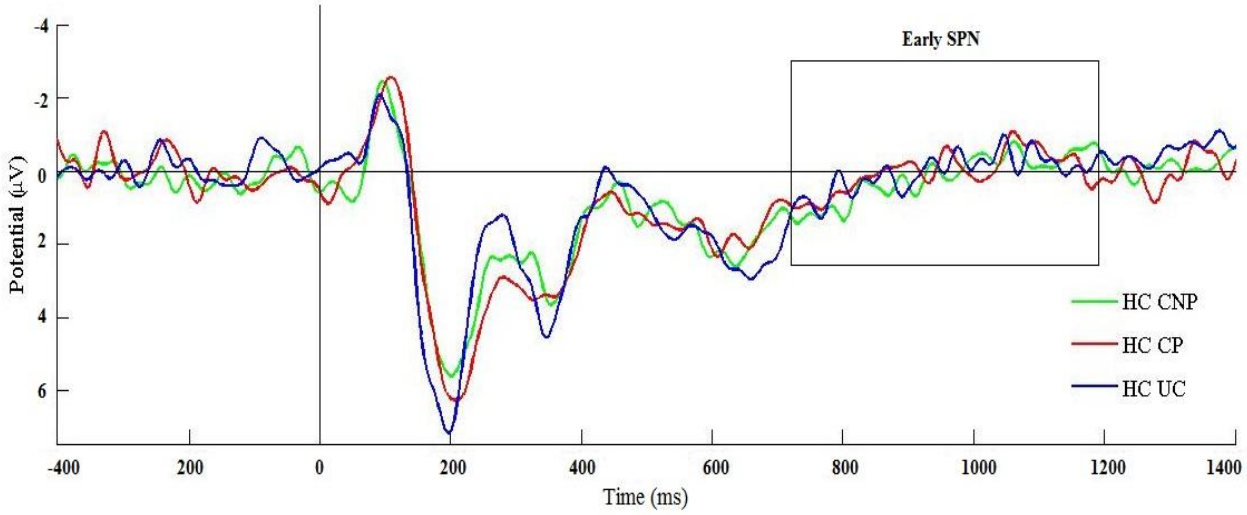

Figure A4

Early SPN mean amplitudes at FCz and surrounding electrode sites for conditions CNP, CP and UC in the MDD group at T2.

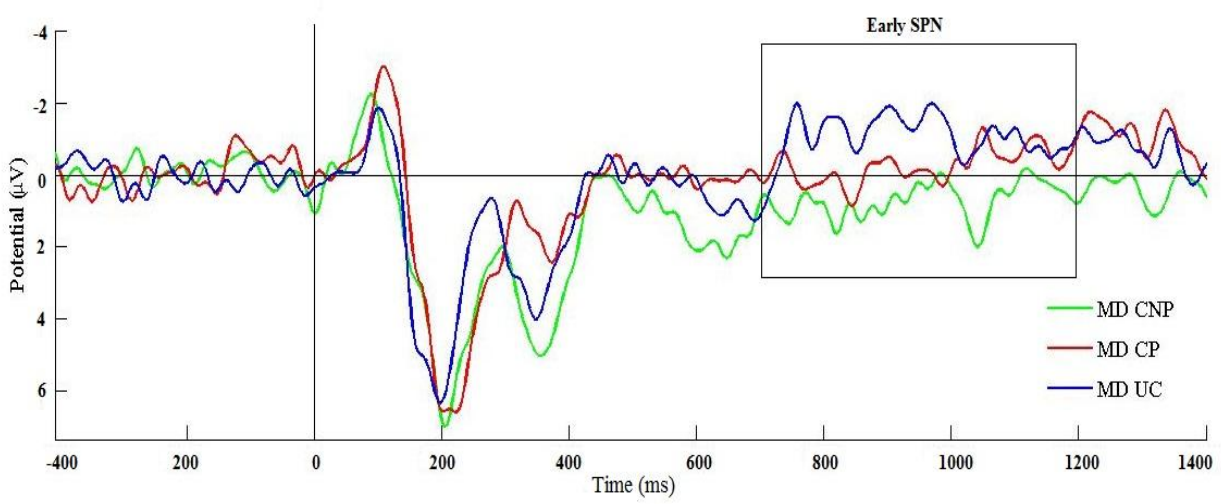

Figure A5

Late SPN mean amplitudes at CPz and surrounding electrode sites for conditions CNP, CP and UC in the HC group at T1.

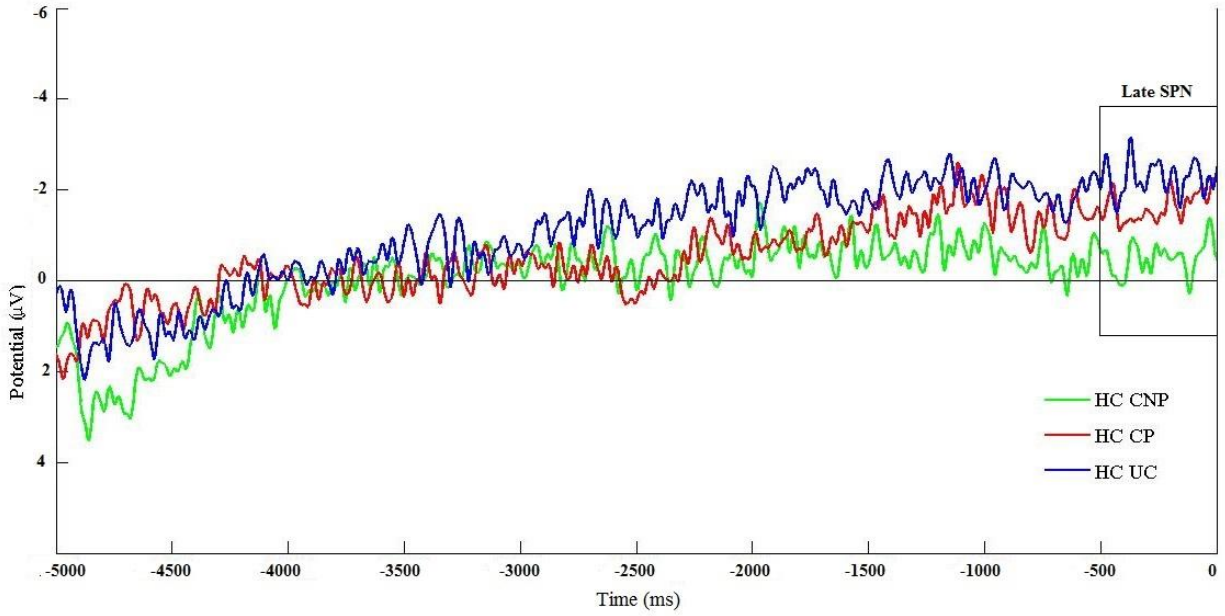

Figure A6

Late SPN mean amplitudes at CPz and surrounding electrode sites for conditions CNP, CP and UC in the MDD group at T1.

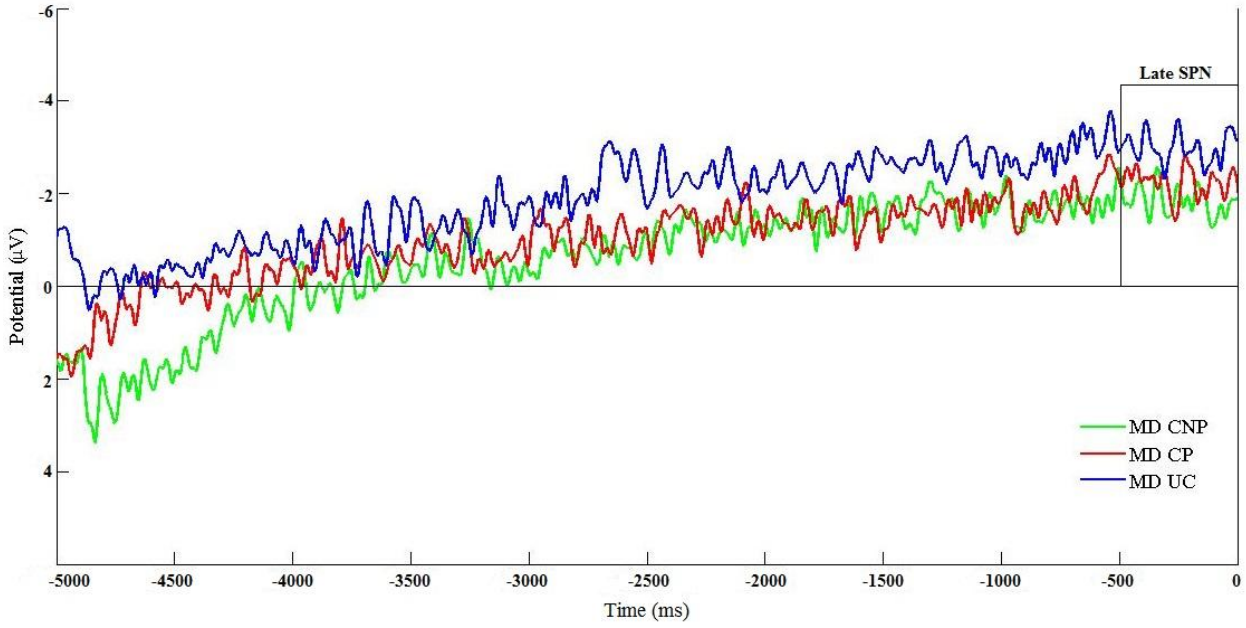

Figure A7

Late SPN mean amplitudes at CPz and surrounding electrode sites for conditions CNP, CP and UC in the HC group at T2.

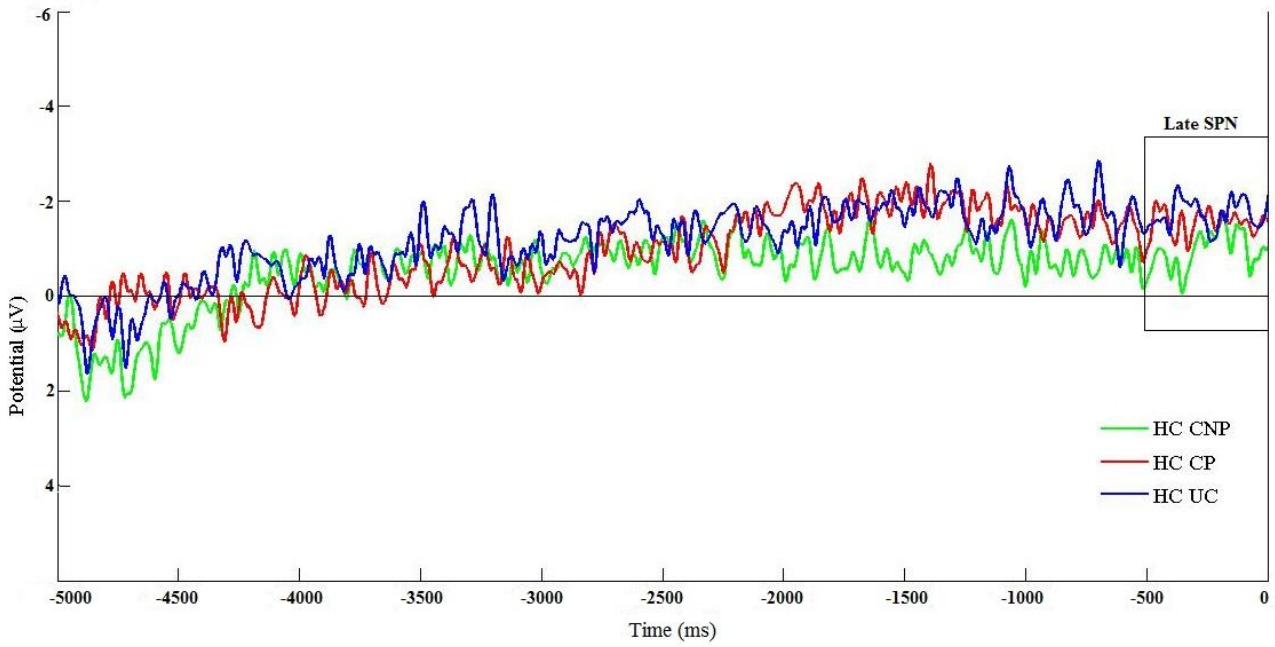

Figure A8

Late SPN mean amplitudes at CPz and surrounding electrode sites for conditions CNP, CP and UC in the MDD group at T2.