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μ-Opioid Modulation of Social Attention: Effects on Eye Gaze and Their Relationship to Autistic Traits and OPRM1 Variation

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Introduction

As social cues such as faces, voices, and body movements have been important throughout human evolution (Emery et al., 2000), faces, and specifically the eyes, are typically prioritized by attention in neurotypical development (Chita-Tegmark, 2016; Frazier et al., 2017). This prioritisation emerges early in development and supports the acquisition of social cognition and communication skills (Dawson et al., 2005; Schultz, 2005). However, there is substantial individual variability in the extent to which social cues are prioritised.

Autism spectrum disorder (ASD) is characterised by differences in social communication and interaction, alongside restricted and repetitive behaviours (American Psychiatric Association, 2013). Importantly, autistic traits are distributed dimensionally in the general population, suggesting that variation in social attention reflects continuous differences in underlying mechanisms rather than discrete diagnostic categories (Grzadzinski et al., 2013). This motivates a focus on the processes that determine how social stimuli are perceived and valued across individuals.

One influential account proposes that variability in social attention reflects differences in the perceived reward value of social stimuli. Neurobiological evidence implicates dopaminergic and μ-opioid systems in assigning motivational and hedonic significance to social cues, thereby influencing attentional allocation (Fields, 2004; Chelnokova et al., 2014; Løseth et al., 2024). Within this framework, gaze toward socially informative features such as the eyes may be driven in part by reward-related mechanisms. μ-opioid signalling may therefore contribute to the motivational salience of social information and may underlie individual differences in social attention.

1. Autism Spectrum Disorder (ASD), Social Behaviour and Social Reward

Individuals with ASD often experience difficulties in spontaneously sharing experiences, interpreting nonverbal social cues, and developing, maintaining, or understanding social relationships. At the same time, ASD is associated with a range of cognitive strengths (Joseph et al., 2002). Individuals frequently exhibit a detail-oriented cognitive style, enhanced pattern recognition, and strong memory abilities in domains aligned with their specific interests, which may contribute to success in areas such as mathematics, science, music, and the visual arts. Historically, early clinical descriptions framed

autism as a rare and distinct disorder, primarily defined by profound social withdrawal and restricted interests. With successive revisions of diagnostic systems, particularly the transition to DSM-5, this view has shifted toward a broader spectrum that captures variability in symptom expression and severity (American Psychiatric Association, 2013). This shift has important implications for research, as it encourages investigation across the full distribution of autistic traits rather than focusing exclusively on clinical populations. Importantly, contemporary accounts conceptualize ASD as a dimensional construct rather than a discrete category, with autistic traits continuously distributed across the general population (Grzadzinski et al., 2013). This dimensional perspective suggests that the mechanisms underlying social behaviour in ASD are not restricted to clinically diagnosed individuals but may also operate, in attenuated form, in non-clinical populations. As a result, investigating variation in autistic traits across the broader population provides a valuable approach for understanding the cognitive and motivational processes that shape social behaviour more generally, including how social stimuli are perceived, prioritized, and experienced as rewarding.

1.1. Behavioural Characteristics of ASD

1.1.1 Restricted or repetitive behaviours, interests, or activities

In addition to social-communication difficulties, ASD is characterized by restricted and repetitive patterns of behaviour, interests, or activities (American Psychiatric Association, 2013). These behavioural patterns can manifest in repetitive motor movements such as hand-flapping or finger flicking, repetitive use of objects (e.g., arranging items in rigid patterns), and repetitive speech (e.g., echolalia or palilalia). Individuals may insist on routines and experience distress when confronted with change or unpredictability. Restricted interests are often highly focused and pursued with unusual intensity, sometimes to the exclusion of other activities.

Another important feature is altered sensory processing, reported in a large proportion of individuals with ASD (Baum et al., 2015). Sensory hypersensitivity may result in strong aversive reactions to otherwise innocuous stimuli such as sounds or touch, whereas hyposensitivity may manifest as reduced responsiveness to sensory input, including pain. Sensory-seeking behaviours, such as a preference for specific textures or repeated sensory experiences, may occur as a compensatory response. These sensory

differences are now formally recognized in diagnostic criteria (American Psychiatric Association, 2013) and may play a crucial role in shaping behaviour, including social engagement.

1.1.2 Difficulties in social communication and social interaction

Deficits in social communication can manifest across a wide range of contexts and vary considerably in severity. Individuals with ASD may experience difficulties initiating or responding to social interactions, maintaining reciprocal conversations, and interpreting others' emotions or intentions. These challenges often extend to the development and maintenance of relationships, where understanding implicit social rules and adapting behaviour to different contexts may be impaired (APA, 2013).

A particularly important component of social interaction is nonverbal communication, which includes gestures, facial expressions, prosody, and eye contact. Individuals with ASD may show reduced, atypical, or absent use of these cues, or may struggle to integrate them effectively with verbal communication. For example, facial expressions may be limited or not aligned with spoken content, and gestures may be used less frequently or in unconventional ways. In some cases, individuals employ compensatory strategies such as camouflaging, where they consciously monitor and imitate social behaviours to appear more neurotypical (Hull et al., 2017). These strategies can include deliberately maintaining eye contact or mimicking others' expressions, which may mask underlying difficulties while increasing cognitive load during social interaction.

Eye contact plays a central role within this broader system of social communication. It supports the identification of others' identity, intentions, and emotional states, contributes to judgments of trustworthiness and affect, and regulates conversational turn-taking (Conway et al., 2008; Itier & Batty, 2009). Beyond these functions, eye contact is fundamental for joint attention, which underpins early social learning and language development (Mundy & Newell, 2007; Dawson et al., 2005). Disruptions in eye contact may therefore have cascading developmental consequences, limiting opportunities for shared attention and reciprocal engagement.

1.1.3 Gaze behaviour

Diagnostic frameworks such as ICD-10, ICD-11, and DSM-5 consistently emphasize atypical eye contact as a central indicator of impaired nonverbal communication in ASD, although they differ slightly in emphasis and formulation. ICD-10 highlights a failure to use eye gaze, facial expressions, and body posture to regulate social interaction, whereas ICD-11 explicitly stresses difficulties in integrating verbal and nonverbal communication, including eye contact (World Health Organization, 1992; World Health Organization, 2019). DSM-5 further refines this by situating atypical eye contact within deficits in both social-emotional reciprocity and nonverbal communicative behaviours (American Psychiatric Association, 2013). Across these frameworks, atypical eye contact is described as reduced, avoidant, poorly integrated, or qualitatively atypical, highlighting its role as a key behavioural marker of ASD.

Empirical research strongly supports this characterization. A robust and well-replicated finding across eye-tracking studies is reduced attention to the eye region of faces in individuals with ASD, often described as an "eye avoidance" pattern (Frazier et al., 2017; Tanaka & Sung, 2016). While these findings establish atypical gaze as a robust behavioural characteristic of ASD, understanding how such patterns are measured and how they vary across contexts requires careful consideration of methodological approaches, which are discussed in Chapter 2.

1.2. The Social Motivation Hypothesis of ASD

As autistic traits have been associated with reduced social motivation (Chevallier et al., 2012; Dawson et al., 2005; Klin et al., 2002; Kohls et al., 2013; Klin, 2023), the Social Motivation Hypothesis posits that reduced sensitivity to social rewards diminishes the drive to seek and maintain social interaction. This, in turn, limits opportunities for social learning and contributes to the emergence of social-communication difficulties over development (Chevallier et al., 2012; Tschida & Yerys, 2021). Supporting behavioural evidence includes reduced spontaneous attention to social stimuli, decreased positive affect in interpersonal contexts, and reduced initiation of social contact from early in life (Chetcuti et al., 2021; Trevisan et al., 2018). Longitudinal studies further link early differences in social motivation to later outcomes in joint attention and language development, as well as to increased autism susceptibility (Stallworthy et al., 2023; Su et al., 2021).

At the neural level, converging evidence points to alterations in social reward processing circuits, including the ventral striatum and associated dopaminergic pathways (Kohls et al., 2013; Scott-Van Zeeland et al., 2010; Bottini, 2018). Importantly, these findings do not support a global deficit in reward processing but rather suggest a more specific alteration in the valuation and motivational salience of social stimuli. For instance, Kohls et al. (2013) reported reduced ventral striatal responses to social incentives, consistent with diminished spontaneous approach behaviour, while Scott-Van Zeeland et al. (2010) found altered neural responses to both social and non-social rewards depending on task characteristics. This pattern indicates that reward processing differences in ASD are context-dependent rather than uniformly reduced.

More recent large-scale neuroimaging work further refines this picture by demonstrating altered functional connectivity within distributed reward networks, including the amygdala, nucleus accumbens, anterior cingulate cortex, and ventromedial prefrontal cortex (Yang et al., 2024). These regions support reward learning, prediction, and motivational engagement, and their altered connectivity has been directly linked to the severity of social communication difficulties. For example, reduced connectivity between the anterior cingulate cortex and both the amygdala and nucleus accumbens, alongside increased connectivity between striatal and insular regions, has been associated with greater impairments in social motivation. Such findings suggest that differences in social behaviour may arise not only from localized dysfunction but from altered integration across large-scale neural systems. The extent to which social motivation differences can be inferred from observable behaviour depends critically on how these processes are operationalized and measured.

1.3 Genetic Factors in ASD

Autism spectrum disorder (ASD) is a neurodevelopmental condition with a complex, multifactorial aetiology arising from interactions between genetic predispositions and environmental influences. Twin and family studies indicate substantial heritability, with estimates ranging from 40% to 80%, pointing to a strong genetic contribution while also highlighting the importance of non-genetic factors (Rylaarsdam & Guemez-Gamboa, 2019). Rather than being caused by a single gene, ASD is now

understood as highly polygenic, involving the combined effects of numerous genetic variants that contribute to individual differences in neurodevelopment (Genovese & Butler, 2020).

One important source of genetic variation involves copy number variations (CNVs), such as deletions or duplications of DNA segments. While certain CNVs are associated with increased likelihood of ASD, they are neither necessary nor sufficient for its development, and identical variants can result in markedly different phenotypic outcomes (Marshall et al., 2008). This variability underscores the importance of gene–gene and gene–environment interactions in shaping autistic traits.

Increasing attention has been directed toward neuromodulatory systems involved in social reward processing, including dopamine, oxytocin, and endogenous opioids. Endogenous opioids will be discussed specifically in a later chapter.

2. Measuring social behaviour in humans (with ASD)

Social behaviour is not directly observable as a single construct but must be inferred from measurable components such as attention, perception, motivation, and interaction patterns. In humans, and particularly in autism research, these processes are most commonly operationalized through behavioural proxies such as gaze allocation, responses to social stimuli, and willingness to engage in social interaction. Importantly, these measures capture partially overlapping but distinct aspects of social functioning, ranging from early perceptual prioritization to higher-order motivational and decision-making processes. This distinction is critical, as differences in observed behaviour (e.g., reduced eye contact) may arise from multiple underlying mechanisms, including altered reward valuation, increased cognitive effort, or differences in learning and prediction.

2.1 Face & emotion processing

In ASD, alterations in face and emotion processing have been widely documented, though they are best understood as differences rather than uniform deficits. While many studies report reduced attention to faces or atypical processing of emotional expressions, findings are heterogeneous and depend on task demands, stimulus properties, and individual differences. Importantly, differences in face processing may reflect downstream consequences of altered attention allocation rather than primary perceptual impairments.

At the same time, gaze behaviour is influenced by multiple interacting factors, including stimulus properties, task demands, and individual differences. Emotional expressions, for example, may modulate gaze allocation, although findings are mixed. Some studies report increased avoidance of the eye region for threatening expressions, suggesting heightened sensitivity to emotionally salient stimuli (Wang et al., 2018), while others find reduced neural sensitivity or no consistent effects (Burt et al., 2017; Corden et al., 2008). These inconsistencies indicate that gaze behaviour is not governed by a single mechanism but likely reflects the interaction of perceptual, affective, and regulatory processes.

2.2 Social reward and motivation

A central question in the study of social behaviour is how social stimuli acquire value and guide attention and action. Influential models of attention propose that gaze allocation is shaped by expected reward value and informational utility (Maunsell, 2004; Schultz, 2006). From this perspective, attending to socially relevant stimuli—such as faces or eyes—can be understood as a value-based decision, reflecting both their informational importance and their intrinsic or learned reward value.

At the neural level, these processes are supported by distributed reward systems involving dopaminergic and opioidergic pathways, particularly within the basal ganglia. These systems contribute to both motivational ("wanting") and hedonic ("liking") aspects of reward processing and influence where attention is directed (Hikosaka et al., 2006). As such, social attention can be conceptualized as an emergent property of reward-based learning and decision-making mechanisms.

Within this framework, atypical gaze behaviour in ASD has been interpreted in different ways. The social salience hypothesis suggests that social stimuli, particularly faces and eyes, are less intrinsically rewarding or informative for individuals with ASD, leading to reduced attention (Grelotti et al., 2002; Neumann et al., 2006). In contrast, the eye avoidance hypothesis posits that eye contact may be experienced as aversive or overly arousing, resulting in active avoidance. These accounts are not mutually exclusive. Reduced social reward value and increased aversive arousal may jointly contribute to atypical gaze patterns.

2.3 Social gaze with eye-tracking

Eye-tracking has become a central tool for quantifying social attention, providing an objective and temporally precise measure of where individuals allocate visual attention. In both clinical and non-clinical populations, gaze behaviour is widely used as a proxy for social interest, information processing, and attentional prioritization. A robust and well-replicated finding across eye-tracking studies is reduced attention to the eye region of faces in individuals with ASD, often described as an "eye avoidance" pattern (Frazier et al., 2017; Tanaka & Sung, 2016). A meta-analysis of 122 independent eye-tracking studies reported that, relative to non-autistic controls, autistic participants devoted more attention to non-social regions of interest and less to eyes and whole faces, especially when stimuli depicted human interactions (Frazier et al., 2017). Effect sizes were largest for eye and whole-face regions within interactive scenes (Hedges' $g \approx 0.47–0.50$). Excessive attention to the mouth has occasionally been reported, particularly in children, but has not consistently replicated. These findings suggest a persistent difficulty in prioritizing socially relevant information over irrelevant or non-social details, a pattern that appears across the autism spectrum and becomes more pronounced when processing dynamic social interactions (Frazier et al., 2017).

This pattern emerges early in development: longitudinal studies show that infants later diagnosed with ASD exhibit a decline in eye fixation within the first months of life (Jones & Klin, 2013; Klin et al., 2020). Across childhood, adolescence, and adulthood, individuals with ASD consistently spend less time fixating on the eyes and more time attending to non-social regions or other facial features such as the mouth (Dalton et al., 2005; Klin et al., 2002; Neumann et al., 2006). Importantly, atypical gaze is also observed in other psychiatric conditions associated with social difficulties, suggesting that it may reflect a transdiagnostic alteration in social information processing rather than a disorder-specific deficit (Dalton et al., 2005; Schilbach, 2013).

Eye-tracking research has employed a wide range of paradigms, including static images, dynamic video stimuli, and increasingly, naturalistic social interactions. While early studies using static or video-based stimuli reliably demonstrated reduced eye fixation (e.g., Klin et al., 2002; Hernandez et al., 2009), later work showed that these differences may be particularly pronounced in dynamic and socially

complex contexts (Speer et al., 2007). More recent studies using real-life interactions have confirmed that atypical gaze patterns persist in ecologically valid settings, with individuals with ASD showing reduced attention to faces and increased gaze toward peripheral regions during social interaction (Noris et al., 2012; Hanley et al., 2015). This convergence across methodologies strengthens the conclusion that reduced eye-directed gaze is a robust feature of ASD.

In screen-based paradigms, participants typically view static images or dynamic videos containing social and non-social stimuli. Neurotypical individuals reliably show a preference for faces and particularly the eye region, even when controlling for low-level visual salience. In contrast, individuals with ASD, on average, show reduced fixation on the eyes and increased attention to non-social or less informative regions. These patterns have often been interpreted as reflecting reduced social motivation or altered reward valuation. However, this interpretation is not uncontroversial. A systematic review found that only a subset of studies fully support the Social Motivation Hypothesis (Bottini, 2018), and first-person accounts indicate that many autistic individuals experience intact or even heightened social motivation, albeit expressed differently (Jaswal & Akhtar, 2018). This raises the possibility that reduced eye contact reflects factors such as increased cognitive load, sensory sensitivity, or differences in social learning rather than diminished interest per se.

Alternative theoretical frameworks emphasize the interactive and contextual nature of social behaviour. The “double empathy” problem suggests that social difficulties arise from mismatches between interaction partners rather than deficits located solely within autistic individuals (Milton, 2012; Crompton et al., 2020). Similarly, the social-interaction-mismatch hypothesis proposes that differences may lie in how social information is integrated and used for prediction and coordination, rather than in its initial perception (Bolis & Schilbach, 2018).

Importantly, methodological advances have begun to address limitations of traditional paradigms. While early eye-tracking studies relied heavily on passive viewing, more recent work incorporates naturalistic and interactive settings, capturing gaze behaviour during real social interactions. These approaches reveal that gaze patterns are context-dependent and dynamically shaped by social demands.

3. Neural Mechanisms of Social Reward

Social behaviour emerges from the interaction of multiple neuromodulatory systems that regulate approach and avoidance tendencies – one of which is the opioid system.

3.1 The opioid system

3.2.1. Endogenous and exogenous opioids

Opioid receptors are G protein–coupled receptors comprising three main subtypes (μ, δ, κ), each associated with distinct endogenous ligands, including endorphins, enkephalins, and dynorphins. Early theoretical work, particularly Panksepp's "Brain Opioid Theory of Social Attachment" (BOTSA), proposed that endogenous opioid activity plays a central role in regulating social bonding and affiliative behaviour (Panksepp et al., 1979). According to this account, reductions in opioid tone during social separation produce distress analogous to withdrawal, motivating social contact, whereas social interaction restores opioid activity and alleviates this state.

Subsequent research has provided substantial support for a key role of μ-opioid receptors in social behaviour. These receptors are involved not only in responses to social distress (e.g., separation or rejection), but also in the processing of positive and affiliative social experiences (Løseth et al., 2014; Pellissier et al., 2017). Importantly, μ-opioid systems extend beyond social behaviour and contribute more broadly to reward processing, particularly hedonic experience, complementing dopaminergic mechanisms of motivation.

3.2.2. Genetic polymorphisms and social behaviour

Genetic studies provide converging evidence for the role of the μ-opioid system in social behaviour. The A118G polymorphism in the OPRM1 gene is the most widely studied functional variant and has been associated with altered opioid receptor binding and signalling (Bond et al., 1998). Behaviourally, this polymorphism has been linked to individual differences in pain sensitivity, reward processing, and responsiveness to opioid antagonists (Ray & Hutchison, 2004; Peciña, 2008).

In particular, the μ-opioid receptor (MOR) system has been implicated in social bonding and the hedonic aspects of social interaction. Investigation of genetic variation within this system, such as polymorphisms in the OPRM, has found that carriers of the G allele show increased sensitivity to social

reward, stronger affiliative tendencies, and reduced avoidance of close relationships (Way et al., 2009; Troisi et al., 2011). Related findings in children suggest enhanced responsiveness to social-emotional cues and greater resilience to adverse social environments (Copeland et al., 2011). These findings are broadly consistent with the view that endogenous opioids modulate the hedonic value of social interactions.

Evidence linking OPRM1 variation specifically to ASD remains mixed. While some studies report associations with social motivation and ASD-related traits (Troisi et al., 2011; LoParo & Waldman, 2015), findings are inconsistent and likely reflect the broader heterogeneity of autism. Nevertheless, these results have contributed to the "opioid hypothesis of autism," which proposes that atypical μ-opioid functioning may underlie alterations in social reward processing (Pellissier et al., 2017).

3.2.3. μ-opioid receptors and social reward processing

Evidence from animal models provides strong causal support for the role of μ-opioid receptors in social behaviour. μ-opioid receptor knockout mice exhibit reduced social interaction and communication, resembling aspects of ASD-like phenotypes (Moles et al., 2004). Conversely, animals carrying gain-of-function variants show increased affiliative behaviour and resilience to social stress (Briand et al., 2015), with similar patterns observed in non-human primates, including effects on mother–infant affiliative behaviour (Barr et al., 2008)

In humans, neuroimaging studies further support the involvement of μ-opioid systems in social reward. Positron emission tomography (PET) studies demonstrate that social touch and laughter trigger endogenous opioid release in brain regions associated with reward and affective processing, including the striatum, insula, and cingulate cortex (Nummenmaa et al., 2016; Manninen et al., 2017).

In the context of ASD, emerging evidence suggests that μ-opioid signalling may contribute to altered social reward processing, although effects remain heterogeneous across individuals. Functional connectivity patterns associated with social preference appear to be modulated by autistic traits, particularly in networks linking visual and reward-related regions. For example, connectivity between the fusiform gyrus and anterior cingulate cortex has been shown to mediate the relationship between

autistic traits and social reward preference, suggesting a neural mechanism through which social stimuli may be experienced as less rewarding (Haffey et al., 2025).

Taken together, these findings position the μ-opioid system as a key neurobiological substrate underlying the hedonic and affective components of social reward, with potential relevance for understanding variability in social motivation and attention in ASD.

4. Pharmacological modulation of the μ-opioid receptors and its effects on social attention

As established earlier, endogenous μ-opioid signalling plays a central role in regulating both social attachment and responses to social distress. Pharmacological blockade of opioid receptors leads to reductions in subjective feelings of social connection and affiliative behaviour, suggesting that endogenous opioid activity contributes directly to the experience of social bonding (Løseth et al., 2024). At the same time, μ-opioid receptor (MOR) activation has been linked to increased engagement with socially salient stimuli such as faces, as well as to enhanced visual attention toward the eye region (Chelnokova et al., 2014; Hsu et al., 2015; Chelnokova et al., 2016). These findings point to a more specific role of the MOR system in shaping social attention, beyond its broader contribution to affective experience.

From the perspective of value-based models of attention, as described in Chapter 2, socially salient features such as faces and particularly the eyes may attract attention to the extent that they are encoded as rewarding. Modulation of the MOR system may therefore directly influence how strongly such stimuli capture attention. Importantly, this framework offers a more mechanistic account of social attention differences than broader constructs such as the social motivation hypothesis, by specifying how reward-related processes translate into observable gaze patterns.

Pharmacological studies provide further support for this interpretation by demonstrating differential effects of opioid agonists and antagonists on social reward processing. Morphine, which primarily stimulates μ-opioid receptors, has been associated with increased motivational salience of socially relevant stimuli, potentially enhancing gaze allocation toward features such as the eyes. In contrast, naltrexone, an opioid antagonist with highest affinity for μ-receptors (and additional effects on κ-receptors), appears to dampen both hedonic and motivational aspects of reward processing (Wardle et

al., 2016; Trøstheim et al., 2022). These opposing effects are consistent with broader models distinguishing between motivational ("wanting") and hedonic ("liking") components of reward, both of which are modulated by the opioidergic system (Berridge & Robinson, 2003; Berridge & Kringelbach, 2015). While μ-opioid activity is generally associated with increased reward sensitivity, κ-opioid receptor systems may exert partially opposing effects, particularly in relation to stress and aversive processing, highlighting the importance of considering receptor-level specificity when interpreting pharmacological findings.

Pharmacological findings further indicate that modulation of μ-opioid systems can influence neural network organization in autistic individuals, potentially linking μ-opioid signalling to sensorimotor processing and broader adaptability, although these effects are not yet fully understood (Dimitrov et al., 2025). Together with genetic evidence on variation in the OPRM1 gene, these findings support the view that individual differences in μ-opioid function may contribute to heterogeneity in social motivation and attention across both clinical and non-clinical populations.

Finally, individual differences in μ-opioid functioning may also be shaped by biological factors such as sex and hormonal status. μ-opioid receptor availability and binding potential have been shown to differ between males and females and to be modulated by hormones such as estradiol (Smith et al., 1998). These differences may influence both baseline sensitivity to social reward and responsiveness to pharmacological manipulation. In line with this, behavioural research suggests that females often show enhanced sensitivity to social cues, including increased attention to the eye region, whereas males may display stronger attentional biases toward sexually relevant stimuli such as attractive faces (Proverbio et al., 2010; Rupp & Wallen, 2009). Such factors may therefore contribute to variability in opioid-related effects on social attention and should be considered when interpreting experimental findings. Taken together, these findings position the μ-opioid system as a key neurobiological substrate underlying both the hedonic and attentional components of social reward.

4. Research question

4.1 Research question

Integrating MOR function, genetic variation, and dimensional autistic traits may extend scientific understanding why social gaze differs within and beyond the autism spectrum. The present study examines how μ-opioid manipulation (via morphine as an agonist and naltrexone as an antagonist) and OPRM1 genotype influence visual exploration of faces, specifically gaze allocation to the eyes across levels of autistic traits. In a previous study, Chelnokova and colleagues (2016) were able to show that pharmacological manipulation of the μ-opioid system altered the visual exploration of faces and overt attention to the eyes in adults. μ-opioid agonism via morphine lead to an increase and antagonism via naltrexone to a decrease in overt visual attention to these socially significant cues. The first goal of this thesis was to investigate the robustness of these findings by using more sophisticated statistical modelling of gaze data and increasing the sample by 19 additional participants. As autistic traits have been associated with reduced social motivation and atypical visual attention to faces, the second research question states: What is the relationship between autistic traits and attention towards the eyes? As its third research question this thesis investigates, whether μ-opioid effects on visual attention interact with individual differences in autistic traits? Finally, there are two exploratory research questions, which will investigate relationships with genetic variation in μ-opioid receptor expression: How does genetic variation, specifically the OPRM1 A118G polymorphism, influence visual attention to faces, and how is this relationship moderated by autistic traits?

4.2 Hypotheses

An array of hypotheses will be tested. The first hypothesis intends to replicate the previous publication with a more appropriate modelling approach and 19 additional participants. In this analysis, we assume that:

H1.1 Morphine (opioid stimulation) will increase the percentage of fixations on the eye region compared to placebo.

H1.2 Naltrexone (opioid inhibition) will decrease fixations on the eye region compared to placebo.

As autistic traits have shown to be associated with reduced social motivation and atypical visual attention to faces in general, especially decreased attention to the socially most salient region of the face, the eyes, the second hypothesis intends to replicate these individual differences in social gaze behaviour.

H2. Higher ASQ scores (reflecting higher autistic traits) will be associated with a lower percentage of fixations on the eye region.

H3. The effects of μ-opioid manipulation (morphine and naltrexone) on visual attention to the eye region will differ as a function of autistic traits (ASQ scores).

This hypothesis is non-directional, because while μ-opioid manipulation (stimulation or inhibition) was shown to influence social reward processing in neurotypical individuals, findings in populations with high autistic traits or ASD are inconsistent (Pellissier et al., 2017; Troisi et al., 2011; Way et al., 2009; Dimitrov et al., 2025) and trials of naltrexone in children with ASC have yielded mixed results in attenuating the core symptoms of autism spectrum conditions (for a review see Roy et al., 2015) This may be because atypical functioning of the μ-opioid system in ASD may alter responses to opioid modulation.

EH4.1 Carriers of the G allele of the OPRM1 A118G polymorphism (A/G) will show a higher percentage of fixations on the eye region compared to A/A homozygotes.

EH4.2. The relationship between the OPRM1 A118G polymorphism and visual attention to the eye region will interact with autistic traits (ASQ scores).

Given that the G allele is associated with increased receptor binding and social reward sensitivity, G allele carriers are expected to show a stronger response to opioid manipulation. Although higher frequency of the G allele has been reported in clinical ASD samples, it may reflect dysregulated opioid signalling rather than straightforward enhancement of social reward.

EH5.1. Under morphine (opioid stimulation), G allele carriers will show greater increases in attention to socially rewarding regions (e.g., eyes) compared to A/A homozygotes.

EH5.2 Under naltrexone (opioid inhibition), G allele carriers will show greater decreases in attention to socially relevant regions compared to A/A homozygotes.

EH5.3: The effects of μ-opioid manipulation and OPRM1 genotype will interact with autistic traits (ASQ scores).

Hypothesis EH5.3 is non-directional, as the effects of the G allele in individuals with high autistic traits remain unclear.

5. Materials and method

5.1 Data collection & dataset

This study was preregistered in January 2025 by x, the supervisor of this thesis, here (10.17605/OSF.IO/GV7MZ). Preregistration occurred after data-collection and dataset merging, but before initiating any statistical analysis. The preregistration sets a systematic analysis pipeline, that was followed, with any deviations from it requiring reporting and reasoning. The dataset was collected as part of a research project conducted by the x group under the supervision of x. The data originates from a randomized, double-blind, placebo-controlled within-subjects design investigating the effects of pharmacological μ-opioid manipulation on social attention. Participants were recruited from the general population and included N = 49 healthy adult males. Initial data-collection resulted in a dataset of 30 participants, on which the original study on μ -opioid manipulation of visual attention to faces and eyes was published. Participants were recontacted and required to complete an additional session, which included the ASQ self-report questionnaire and the DNA sampling. Further, 19 additional participants were recruited, which completed the same tasks as the original group. To allow for statistical analysis of the genetic data, these 19 additional participants were pre-screened for the OPRM1 A118G polymorphism, which was of interest. Since A/A-carriers are a lot more common in the general population, A/G carriers were oversampled in the additional recruitment phase. These datasets were then merged to allow for the analysis in this thesis. Merging was verified by replicating the originally published analysis. This was mostly successful for the fixation time data in percentages, with small, expected deviations from the original results. These deviations are likely due to the data being distributed across several sources and the time elapsed since initial collection, which made reconstruction of the original dataset more challenging.

Table 1 shows the distribution of the two between-subject predictors in this study in the two subsamples and the full sample. Mean ASQ scores were very close across samples with M = 16.54, with a standard deviation of SD = 8.17, in the original sample and M = 17.17, SD = 6.39 in the additional sample, resulting in a mean of M = 16.78, SD = 7.46 in the total sample. This matches the distribution found in nonclinical samples, for example a comprehensive systematic review of 73 articles involving 6,934 non-clinical participants found a mean AQ score of 16.94 (Ruzich et al., 2015), a more recent study collected a mean ASQ score of 17.0 in its nonclinical group of 6,934 participants (Yoshinaga et al., 2023). In the table, the oversampling of G-carriers in the additional dataset is prominent, resulting in an almost uniform distribution of genotype in the total sample. The distribution in the original dataset more closely resembles natural distribution in the general population, with a large Swedish study with 18,936 participants finding that 77% had the A/A genotype, while the remaining 23% carried at least one G allele (Persson et al., 2019). Very few studies have investigated the distribution of the OPRM1 A118G polymorphism in autistic individuals. One study on a clinical population of 76 children with verbal and non-verbal ASD found a distribution of only 2.63% with the A/A genotype and 97.37% with either A/G or G/G (Hamilton, 2020). This large difference of distribution compared to the general population suggests a link between genotype and condition and may be seen as part of the rationale that warrants investigating this association in a subclinical sample.

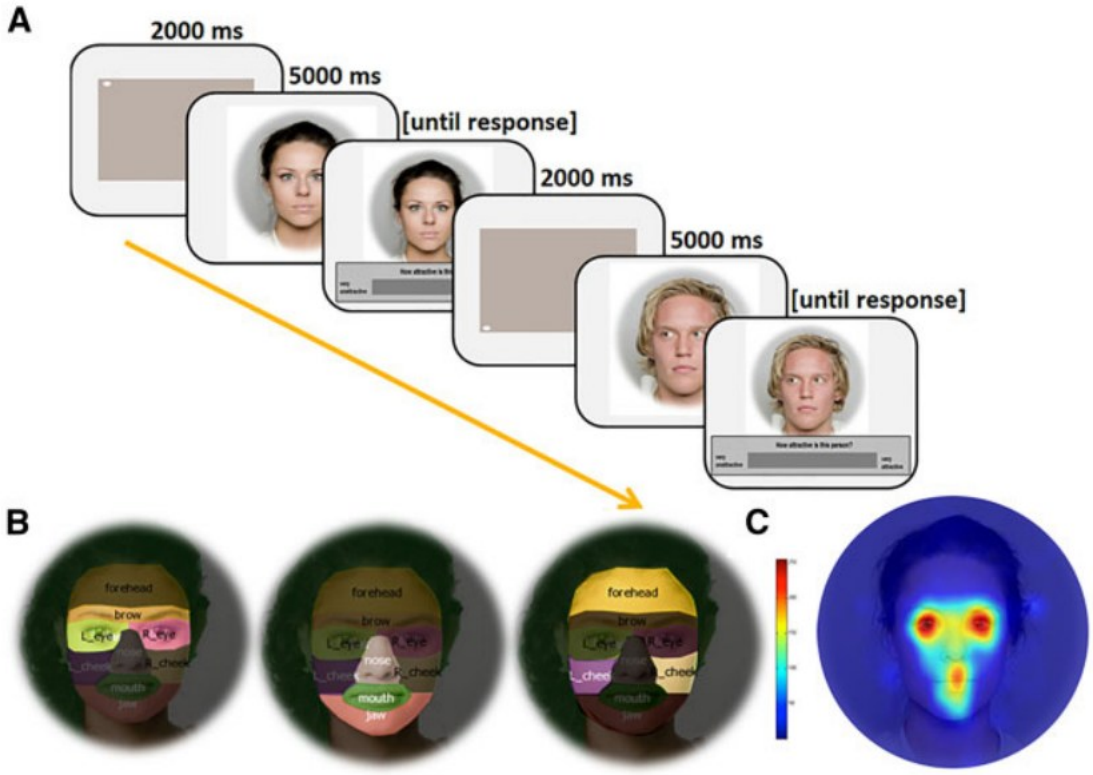
Table 1. Sample overview and descriptives of main predictors

Variable	Original (n = 30)	Additional (n = 19)	Total (N = 49)
ASQ score (M, SD)	16.54 (8.17)	17.17 (6.39)	16.78 (7.46)
Genotype (N, %)	A/A: 25 (83.33%) A/G: 5 (16.67%)	A/A: 2 (10.53%) A/G: 17 (89.47%)	A/A: 27 (55.1%) A/G: 22 (44.9%)

As argued by Chelnokova and colleagues (2016), to avoid potential drug interaction with circulating levels of estradiols and GnRH pulsability in females (Smith et al., 1998), only male participants were included in the test sample. Each participant completed three experimental sessions during which they

were randomly assigned to receive 10 mg of morphine as the opioid stimulation, 50 mg of naltrexone as the opioid inhibition or a placebo. During each session, participants completed an eye-tracking task to measure visual attention to faces, a visual overview, taken from Chelnokova et al. (2016) is provided in Figure 1. Visual attention to faces was measured using an eye-tracking device (R.E.D., SensoMotoric Instruments, sampling rate 250 Hz). Participants viewed 40 neutral faces (20 male, 20 female) sampled to ensure an equal distribution in attractiveness (3 levels) from the Oslo Face Database, each displayed for 5 seconds. Faces were shown with either direct gaze or averted gaze. Raw eye-tracking data was pre-processed using manually delineated AOI masks to segment fixation time into the relevant regions (eyes and brows; forehead and cheeks; nose, mouth and jaw; whitespace and hair).

Figure 1. Task design and AOI regions



Study overview taken from Chelnokova et al. (2016). (A) Timeline showing averted and direct gaze, face gender and the attractiveness rating task after stimulus presentation (B) Map of AOI regions (C) Heatmap showing the cumulative fixation pattern to one face observed in the current study

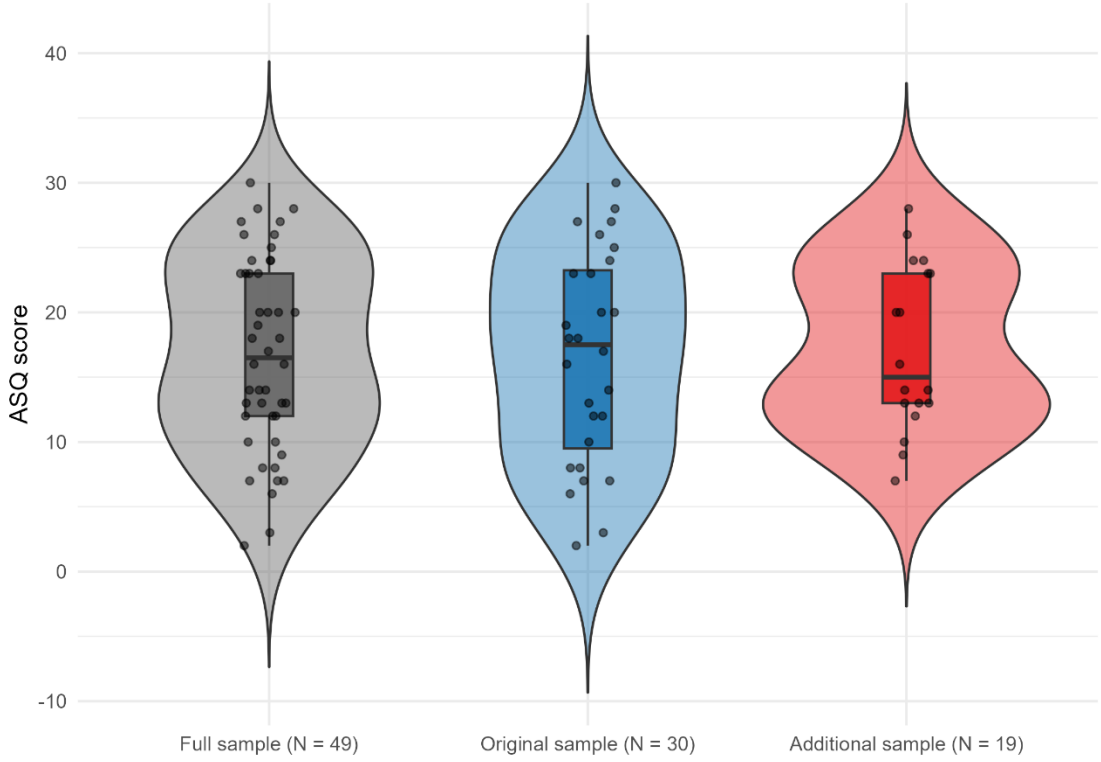
In this analysis only the percentage of total fixation time to the eye-region was analysed. The number of eye-fixations to the whole face and fixation time percentages of the other AOIs, which were analysed

on the original dataset by Chelnokova et al. (2016) were not analysed here. The rationale was that the eyes can be deemed the most salient social stimulus of the face and the eye-region had shown the highest informational value compared to the other AOIs in the original study. Further, ASC and autistic traits have been shown to be associated with an avoidance of direct eye contact, and although not the same, attention to the eyes can be seen as the best proxy of this available in a static computer image paradigm, as used in this study. Participants also completed a self-report assessment of autistic traits (via the Autism Spectrum Quotient, ASQ). DNA samples were provided, and genotyping was performed for the OPRM1 A118G polymorphism using TaqMan SNP genotyping assays. A more detailed description of the procedure can be found in the paper by Eikemo et al. (2016). The analysed dataset includes the eye-tracking data (the fixation time percentages for each AOI), the three drug conditions as a within-subject factor, ASQ scores, genetic information (OPRM1 A118G polymorphism) and experimental variables, which are used as control variables in the analysis, such as gaze direction and face stimulus characteristics. The data collection procedures are described more extensively in the previous publication by Chelnokova and colleagues (2016).

5.2 Variables

The dependent or outcome variable was Fixation Time Percentage, a continuous variable, defined as the proportion of total fixation time spent on predefined facial areas of interest (AOIs), calculated as a percentage of total fixation duration. As mentioned before only the eye-region was analysed. Main predictors were Drug, ASQ and Genotype. Drug was coded as a categorical within-subject factor with 3 levels, with Morphine (10 mg) intended to produce μ-opioid receptor stimulation, Naltrexone (50 mg) intended to produce μ-opioid receptor inhibition, and Placebo serving as the baseline condition. ASQ was included as a continuous predictor with a range of 0–30, indexing sub-clinical individual differences in autistic traits measured by the Norwegian validated full version of the Autism Spectrum Quotient (ASQ) questionnaire with 50 items, where higher scores indicate greater levels of autistic traits. The originally proposed clinical cut-off score by Baron-Cohen et al. (2001) was 32 or more out of 50. With a maximum score of 30 in this dataset, the sample can be labelled as healthy. The distribution in the subsamples and total sample is displayed in Figure 2 via violin plots.

Figure 2. ASQ score distribution by sample



Genotype was included as a categorical predictor with two levels, capturing genetic variation in the OPRM1 A118G polymorphism, with "A" indicating homozygous A-allele carriers (A/A) and "G" indicating heterozygous G-allele carriers (A/G). The control variables included in the analysis were Gender, Gaze direction, Attractiveness level, Stimulus order, Image set and Session number. Gender being a categorical variable with two levels, indicating the gender of the face stimuli (male vs. female). Gaze direction was also categorical with two levels, describing whether the gaze in the facial stimuli was direct (eyes looking straight at the observer) or averted (eyes directed away); Attractiveness level had three levels, indicating whether each facial stimulus had been pre-categorized as very attractive, attractive, or less attractive based on ratings from an independent sample; Stimulus Order was continuous, representing the sequential order in which face stimuli were presented within each session. Image sets had six levels, indicating the specific subset of images presented during the task. Session number represented whether the data was obtained from session 1, 2, or 3.

5.3 Missing data

The dataset contained some missing values in key variables. For the ASQ (Autism Spectrum Quotient), 3 participants (approximately 6% of the sample) were missing questionnaire scores. For the Drug factor, 3 participants (6%) were missing data for a single drug condition, while having data for the remaining conditions. At the trial level, 3 participants have incomplete trial data, missing 4, 16, and 20 of 480 total trials, respectively. Since the primary analyses was conducted using generalized linear mixed-effects models, which can incorporate all available observations without requiring complete data for every participant, condition, or trial, all participants were retained in the analyses, and the models mitigate missingness at the observation level by estimating parameters based on the available data.

5.4 Statistical outliers

During merging of the dataset and preregistration of the study, the decision was made that no outliers would be removed from the dataset. This decision was based on the bounded nature of the dependent variable (fixation percentages, constrained between 0 and 1), the categorical nature of key predictors such as Genetics and Drug, and the limited range and absence of extreme values by design for ASQ scores, especially in a non-clinical sample. Given these characteristics, the data was expected to contain no meaningful statistical outliers, and all observed values were retained in the analyses.

5.5 Statistical models

For all hypotheses, the primary statistical model was a beta regression estimated with the glmmTMB package in R. This approach was decided on during preregistration and deemed appropriate because the dependent variable (fixation time percentage) represented proportions constrained between 0 and 1. The models included fixed effects for the main predictors (ASQ, drug condition, genotype) and random intercepts for participants to account for the within-subjects design. Including drug as a by-participant random slope to account for individual differences in drug response was a decision dependent on inference criteria, meaning if model-fit was significantly improved by the random slopes they would be included. Post-hoc tests were conducted with the emmeans package in R. All models additionally included the control variables, that were already described above (gender of the face stimulus, gaze

direction, attractiveness level, stimulus order, image set, session number) but are omitted from the model formulas here for simplification.

The analyses only included fixation time percentages to the eye region, although it was preregistered that results for the mouth region and the rest of the face would be reported when effects reached statistical significance. Hypotheses H1.1 and H1.2 on drug effects on eye fixation were preregistered to be tested only in the subset of 19 participants whose data had not been included in the previously published analysis. However, at the time of preregistration, no power analysis had been conducted for this limited subset, and in fact the sample was insufficient to reveal the expected effects. Results were reported as preregistered for completeness, but H1.1 and H1.2 were tested on the entire dataset. H2 predicted that higher ASQ scores would be associated with lower fixation percentages on the eye region, and EH4.1 predicted that G-allele carriers would show higher fixation percentages on the eye region than A/A homozygotes. These hypotheses were evaluated in an additive model with no interaction terms, with post-hoc tests comparing drug levels, estimating simple slopes of ASQ, and comparing genotype groups (**model 1**).

$$\text{Fixation Time Percentage} \sim \text{Drug} + \text{ASQ} + \text{Genotype} + (1 + \text{Drug} \mid \text{Participant})$$

To examine two-way interactions, H3 predicted that the effects of drug condition on fixation percentages would differ as a function of ASQ scores, and this was tested in a model including a Drug × ASQ interaction (**model 2**):

$$Fixation\ Time\ Percentage \sim Drug * ASQ + Genotype + (1 + Drug \mid Participant)$$

This was followed by post-hoc comparisons between drug conditions at specified marginal levels of ASQ. The exploratory hypothesis EH4.2 predicted that the association between ASQ scores and fixation percentages would differ by genotype; this was tested in a model including an ASQ × Genotype interaction, with post-hoc analyses focusing on simple slopes of ASQ within each genotype group (**model 3**):

$$Fixation\ Time\ Percentage \sim Drug + ASQ * Genotype + (1 + Drug \mid Participant)$$

Further exploratory hypotheses concerned drug × genotype effects on attention to the eyes. Under morphine (opioid stimulation), EH5.1 predicted greater increases in attention to the eyes among G-allele

carriers, whereas under naltrexone (opioid inhibition), EH5.2 predicted greater decreases in attention to the eyes among G-allele carriers. The predictions of EH5.1 for stronger morphine stimulation effects and EH5.2 for stronger naltrexone inhibition effect in G-carriers were examined in a model including a Drug × Genotype interaction, with post-hoc tests comparing drug effects (morphine vs. placebo and naltrexone vs. placebo) within each genotype group (**model 4**):

$$Fixation\ Time\ Percentage \sim Drug * Genotype + ASQ + (1 + Drug | Participant)$$

Finally, the three-way interaction hypothesis EH5. was evaluated using a model that included the full Drug × Genotype × ASQ interaction, and post-hoc analyses estimated simple slopes of ASQ for each combination of drug condition and genotype (**model 5**):

$$Fixation\ Time\ Percentage \sim Drug * Genotype * ASQ + (1 + Drug | Participant)$$

5.6 Statistical power

At the time of preregistration, a priori power analyses were conducted using the pwr package in R, assuming an α-error probability of 0.05, a sample size of 49, one tested predictor, and a total of seven predictors (including interaction terms), with degrees of freedom defined as sample size minus the total number of predictors minus one. For the most complex model including the three-way interaction, this approach yielded estimated power values of $1 - \beta = 0.97$ for a large effect ($f^2 = 0.35$), $1 - \beta = 0.70$ for a medium effect ($f^2 = 0.15$), and $1 - \beta = 0.15$ for a small effect ($f^2 = 0.02$). Thus, the full sample had roughly adequate statistical power to detect medium to large effects in the most complex model. The small effects expected in the genotype analysis potentially limiting the power of these analyses will be a topic of discussion below.

Conversely, for the preregistered subsample of n = 19 used to test H1.1 and H1.2, the resulting power estimates dropped substantially, to 0.49 for a large effect, 0.25 for a medium effect, and 0.08 for a small effect. This indicates that the subsample analyses were clearly underpowered, even for detecting effects in the medium-to-large range. Consequently, non-significant findings for H1.1 and H1.2 should be interpreted with caution, as they may reflect insufficient statistical power rather than true absence of an effect.

5.7 Inference criteria

As preregistered, all statistical tests used a two-tailed significance level of $p = 0.05$. Model fit was assessed with information criteria (AIC, BIC) and LRTs were used to compare nested models. For hypotheses involving multiple conditions or levels (e.g., Drug: Morphine, Naltrexone, Placebo), corrections for multiple comparisons were applied using the Tukey method as implemented in the emmeans package in R.

Across all five likelihood ratio tests, models including a random slope for Drug by participant fit the data significantly better than the corresponding random-intercept-only models, indicating substantial between-participant variability in drug effects. Specifically, the random-slope model provided a superior fit for Model 1, $\Delta\chi^2(5) = 2162.20$, $p < .001$; Model 2, $\Delta\chi^2(5) = 2126.40$, $p < .001$; Model 3, $\Delta\chi^2(5) = 2162.50$, $p < .001$; Model 4, $\Delta\chi^2(5) = 2141.80$, $p < .001$; and Model 5, $\Delta\chi^2(5) = 2077.00$, $p < .001$. The random effects structure further suggested substantial inter-individual heterogeneity in drug response. Although this supports modelling Drug as a random slope, it also implies a more demanding analytic setting in which detecting subtle between-subject genetic effects may require substantially larger samples.

Comparisons among the random-slope models themselves further showed that adding interaction terms did not significantly improve model fit. The inclusion of the Drug × ASQ interaction did not improve fit over the simpler main-effects model, $\Delta\chi^2(2) = 0.97$, $p = .615$. Likewise, the model including ASQ × Genetics did not fit significantly better than the Drug × ASQ model, $\Delta\chi^2(1) = 0.60$, $p = .439$, and the model including Drug × Genetics did not significantly improve fit over the ASQ × Genetics model, $\Delta\chi^2(1) = 1.79$, $p = .181$. Adding the three-way interaction Drug × Genetics × ASQ also did not improve model fit, $\Delta\chi^2(5) = 3.05$, $p = .692$. Importantly, the direct comparison between the simplest slope model (Model 1) and the model including the Drug × Genetics interaction (Model 4) was also nonsignificant, $\Delta\chi^2(2) = 2.17$, $p = .339$, further indicating that the additional interaction term was not warranted.

Inspection of the information criteria for the slope models supported the same conclusion. Among the candidate slope models, Model 1 showed the lowest AIC and BIC (AIC = -6969.30, BIC = -6811.20), followed by Model 3 (AIC = -6967.60, BIC = -6802.90), Model 4 (AIC = -6967.40, BIC = -6796.10),

Model 2 (AIC = -6966.20, BIC = -6795.00), and Model 5 (AIC = -6960.50, BIC = -6756.30). Because lower AIC and BIC values indicate better relative model fit, these indices suggest that Model 1 provided the best model fit.

5.8 Assumption violation / model non-convergence

Model assumptions were assessed using the DHARMa and performance packages in R, with particular attention to homoscedasticity, residual distributions, and multicollinearity. Any substantial assumption violations and corresponding diagnostic plots were planned to be reported in the supplementary materials. There was no evidence of singularity or problematic multicollinearity for the primary models, although higher-order interaction models showed elevated variance inflation factors. Simulation-based diagnostics indicated significant deviations from the expected residual distribution, including evidence for underdispersion and an increased proportion of outliers across all models. This pattern suggests some degree of model misspecification or remaining unexplained structure in the data. However, given the consistency of this pattern across model specifications and the robustness of the main effects, these deviations were not considered to warrant deviations from the preregistered analysis pipeline.

6. Results

6.1 Hypothesis I – Replication

H1.1 Morphine (opioid stimulation) will increase the percentage of fixations on the eye region compared to placebo.

H1.2 Naltrexone (opioid inhibition) will decrease fixations on the eye region compared to placebo.

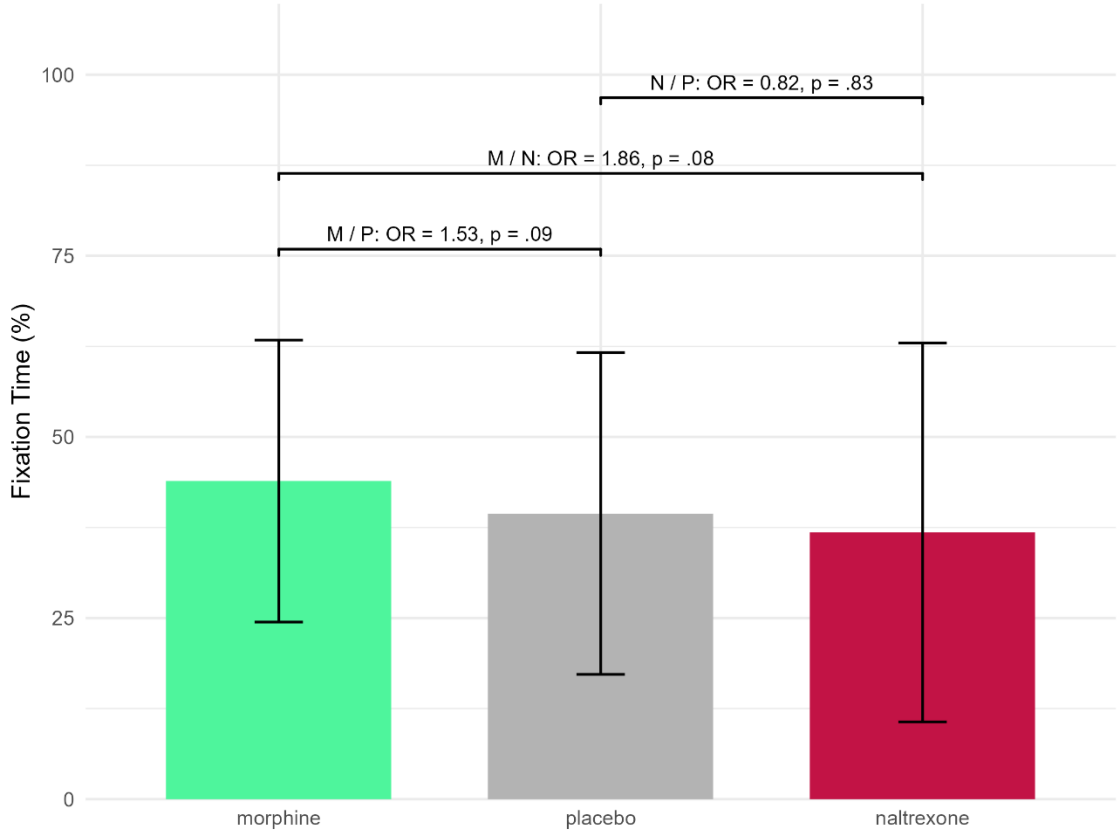
The first hypothesis, split up into the stimulation and inhibition drug condition, was preregistered to be tested in the additional 19 participants only. We will therefore report these results first.

The omnibus test showed a significant main effect of Drug on the proportion of fixations directed to the eye region, $\chi^2(2) = 8.34$, $p = .015$. Estimated marginal means indicated that fixation proportions were highest in the morphine condition ($M = .520$, $SE = .036$, 95% CI [.450, .590]), followed by placebo ($M = .414$, $SE = .064$, 95% CI [.297, .542]) and naltrexone ($M = .368$, $SE = .076$, 95% CI [.235, .524]).

However, Tukey-adjusted pairwise comparisons in Figure 3 showed that neither the difference between morphine and placebo nor the difference between naltrexone and placebo reached significance. Specifically, morphine did not significantly increase fixations to the eye region relative to placebo, OR = 1.53, $z = 2.12$, $p = .086$, and naltrexone did not significantly decrease fixations relative to placebo, OR = 0.82, $z = -0.58$, $p = .832$.

For the fixed effect itself, the model coefficient for morphine was significant relative to placebo on the logit scale, $b = 0.43$, $SE = 0.20$, $z = 2.12$, $p = .034$, whereas naltrexone was not, $b = -0.20$, $SE = 0.34$, $z = -0.58$, $p = .563$. The additional dataset alone was too underpowered to replicate the results, with the morphine effect showing a tendency towards significance, but both H1.1 and H1.2 were not supported.

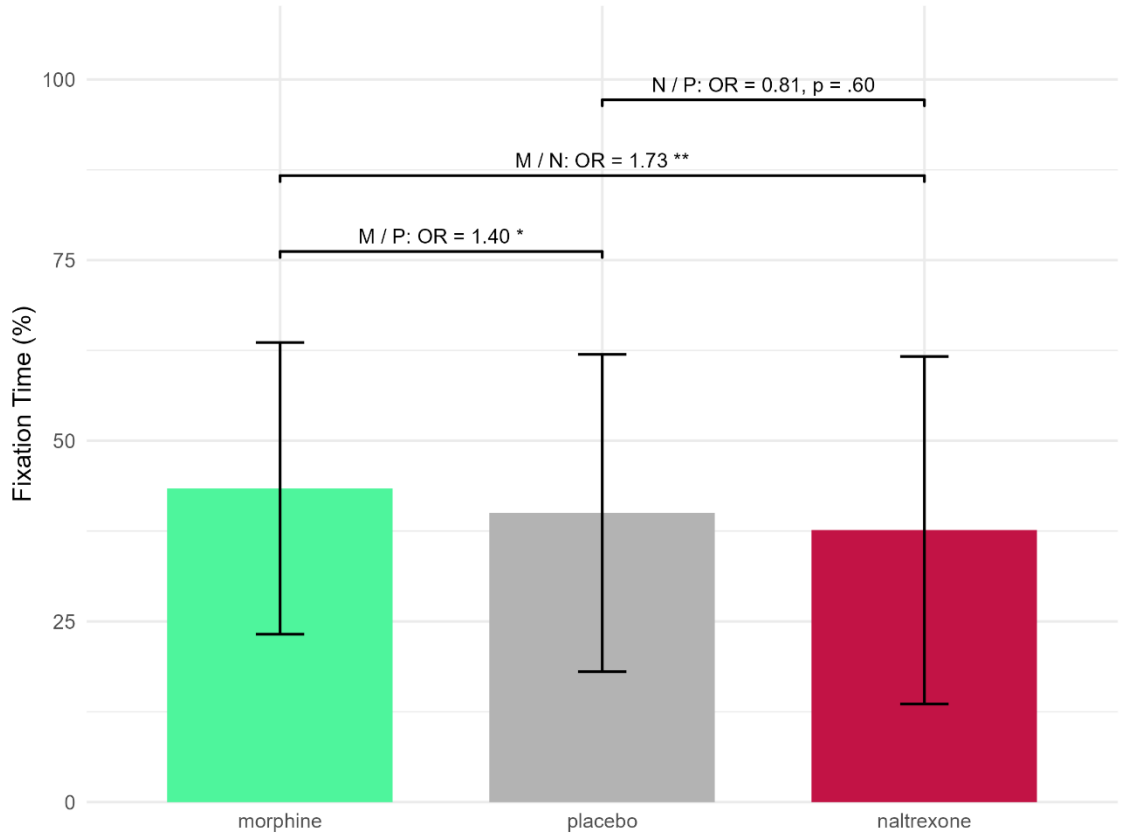
Figure 3. Tukey-adjusted contrasts for drug effect (additional dataset – 19 participants)



Running the same model on the entire dataset of 49 participants supports the claim that the morphine effect is diminished by a lack in power. Tukey-adjusted pairwise contrasts in Figure 4 showed that morphine led to a significantly higher proportion of fixations on the eye region than placebo, OR = 1.40,

z = 2.35, p = .0495, 95% CI [1.06, 1.87], supporting H1.1. In contrast, naltrexone did not significantly differ from placebo, OR = 0.81, z = -0.96, p = .600, providing no support for H1.2. Additionally, morphine produced significantly higher fixation proportions than naltrexone, OR = 1.73, z = 2.93, p = .010, 95% CI [1.20, 2.48].

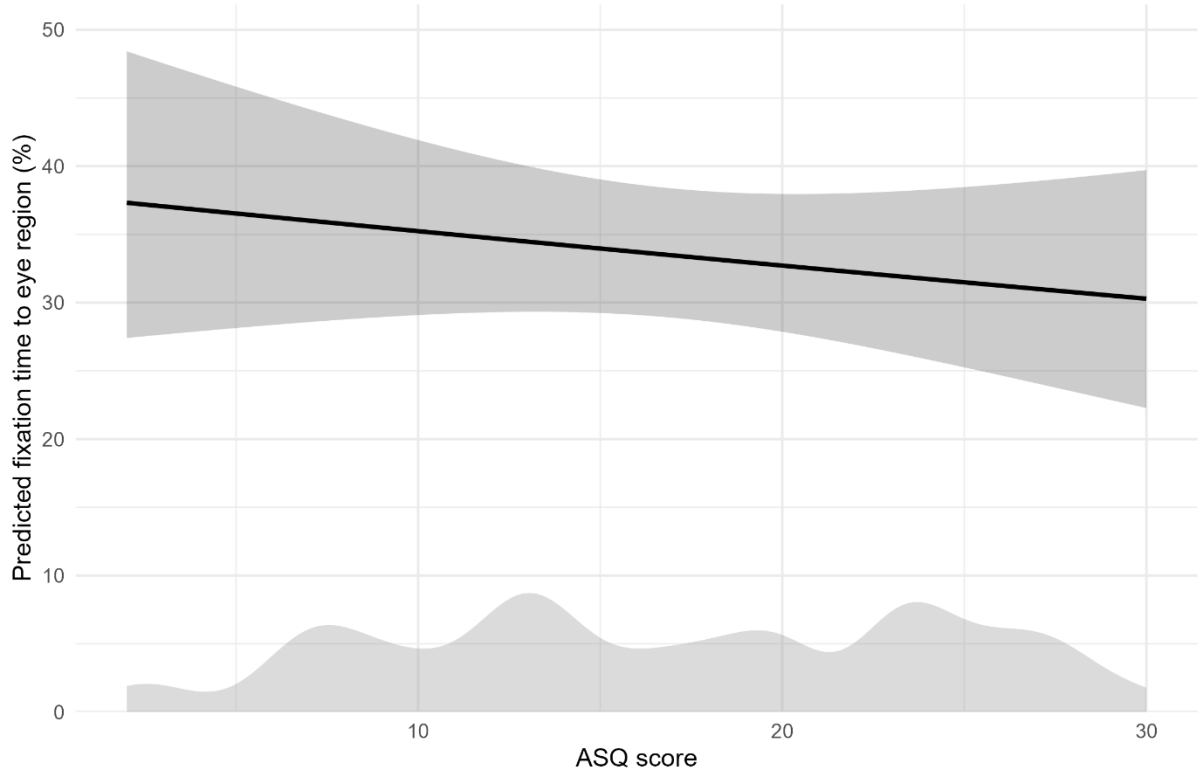
Figure 4. Tukey-adjusted contrasts for drug effect (full dataset – 49 participants)



6.2 Hypothesis II - ASQ

For H2, there was no significant association between autistic traits and the proportion of fixations on the eye region. In the main-effects model, ASQ did not significantly predict eye-region fixations, b = -0.011, SE = 0.014, z = -0.81, p = .416, $\chi^2(1)$ = 0.66, p = .416. Although the coefficient was descriptively negative, it was minimal. The regression line in Figure 5, shows the expected negative association between fixation time to the eye and ASQ score, but regression lines showing a positive effect or no effect can be drawn within the grey confidence area around it, illustrating insignificance. Therefore, H2 is not supported.

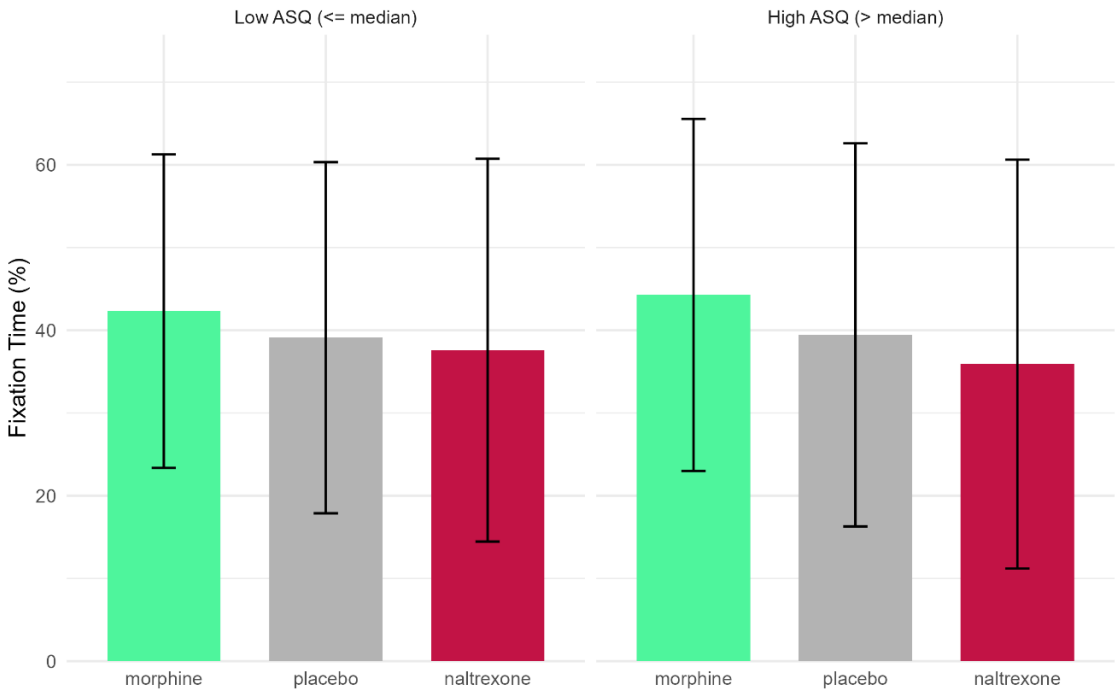
Figure 5. Eye-region fixation by ASQ score



6.3 Hypothesis III – Drug and ASQ interaction

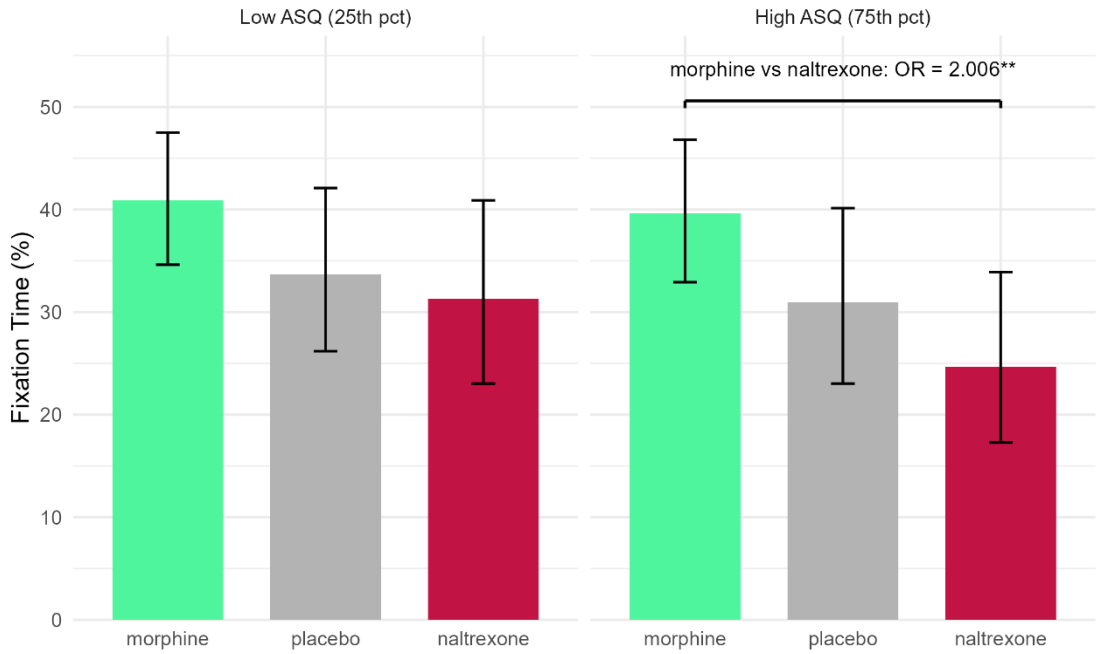
For H3, the results did not support the prediction that the effects of morphine and naltrexone on eye-region fixations would vary as a function of autistic traits. In the interaction model, the Drug × ASQ term was not significant, $\chi^2(2) = 0.99$, $p = .609$. Consistent with this, neither the morphine × ASQ interaction, $b = 0.007$, $SE = 0.021$, $z = 0.32$, $p = .750$, nor the naltrexone × ASQ interaction, $b = -0.018$, $SE = 0.029$, $z = -0.64$, $p = .520$, reached significance. Splitting the ASQ scores by median in Figure 6 led to no significant post-hoc contrasts between the drug conditions.

Figure 6. Drug effects at low vs high ASQ (ASQ was median-split)



Descriptively you can see a trend of greater drug effects in the High ASQ group, which becomes more pronounced when looking at the lowest and highest quartiles of ASQ (lower or equal to 25th percentile and 75th percentile and higher) shown in Figure 7. The only significant difference in drug effects was shown between morphine and naltrexone in the 75th percentile (high) ASQ subgroup, OR = 2.01], $z = 2.92$, $p = .010$, 95% CI [1.26, 3.21]. The overall non-significant interaction indicates that these apparent differences should not be interpreted as reliable moderation by autistic traits. Thus, H3 was not supported.

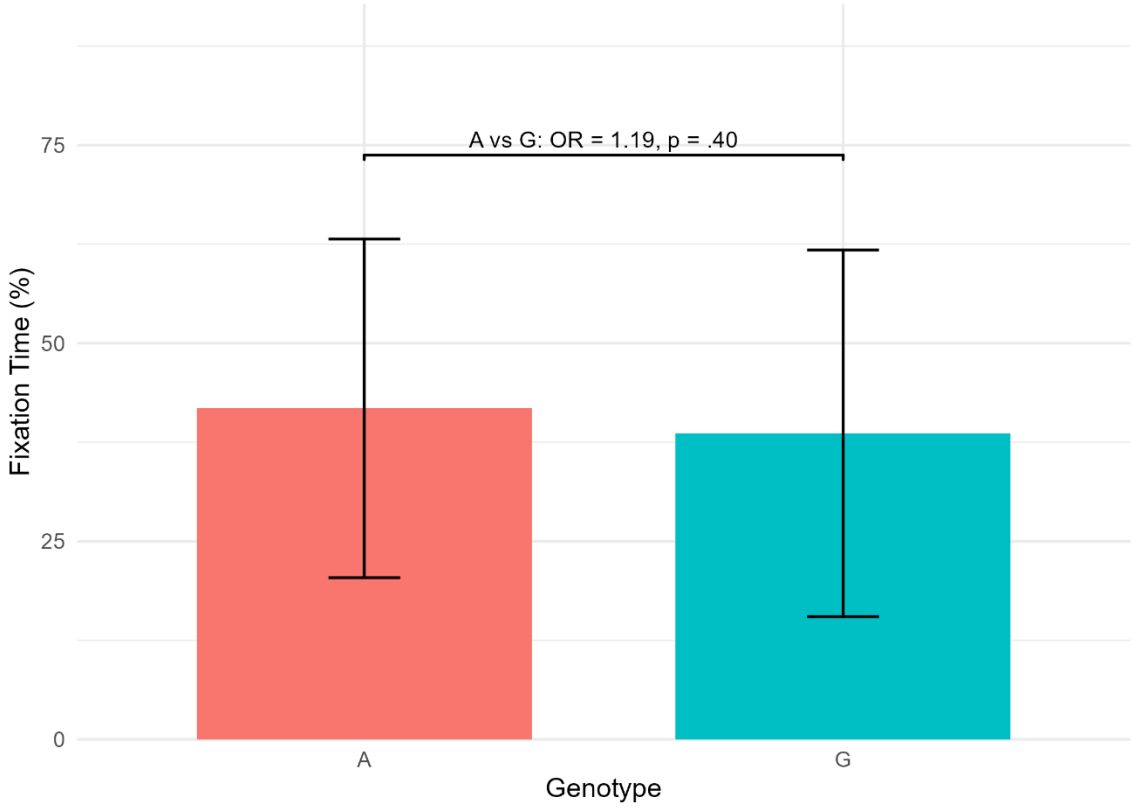
Figure 7. Drug effects at low vs high ASQ (Percentiles)



6.4 Exploratory Hypothesis IV

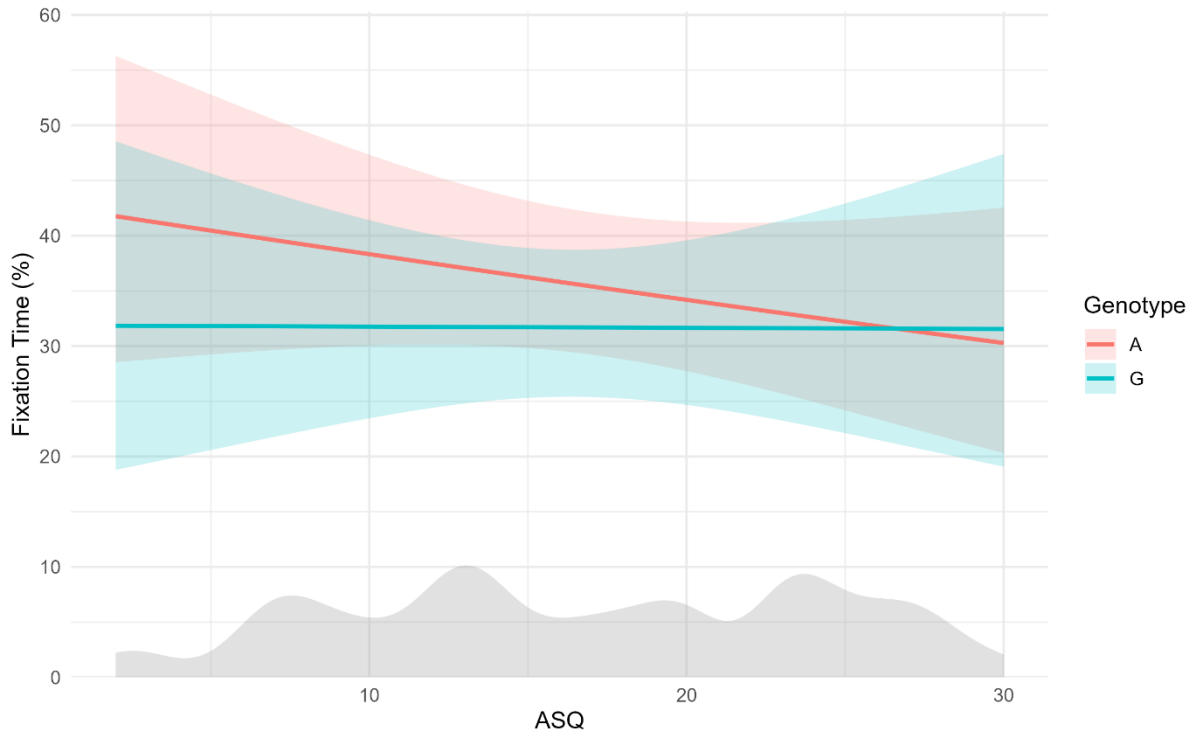
For EH4.1, the hypothesis that carriers of the G allele would show a higher percentage of fixations on the eye region than A/A homozygotes was not supported. In the model, Genetics did not significantly predict eye-region fixations, $\chi^2(1) = 0.71$, $p = .399$. Consistent with this, the coefficient for the G group was non-significant, $b = -0.177$, $SE = 0.210$, $z = -0.84$, $p = .399$. Estimated marginal means indicated descriptively lower fixation proportions for G-allele carriers ($M = .316$, $SE = .034$, 95% CI [.253, .386]) than for A/A homozygotes ($M = .355$, $SE = .033$, 95% CI [.293, .422]). The Tukey-adjusted contrast was not significant, OR = 1.19, $z = 0.84$, $p = .399$. Thus, EH4.1 was not supported; if anything, the descriptive pattern, as can be seen in Figure 7, was opposite to the predicted direction.

Figure 8. Eye-region fixation by genotype



For EH4.2, the hypothesis that the association between OPRM1 genotype and visual attention to the eye region would vary as a function of autistic traits was not supported. In the model including the ASQ × Genetics interaction, the interaction term was not significant, $\chi^2(1) = 0.38$, $p = .540$. Consistent with this, the coefficient for the interaction was small and non-significant, $b = 0.017$, $SE = 0.028$, $z = 0.61$, $p = .540$. Neither the main effect of ASQ, $\chi^2(1) = 0.66$, $p = .415$, nor the main effect of Genetics, $\chi^2(1) = 0.72$, $p = .397$, was significant. Estimated marginal means showed descriptively similar fixation proportions at the mean ASQ level for A/A homozygotes ($M = .355$, $SE = .033$, 95% CI [.293, .422]) and G-allele carriers ($M = .317$, $SE = .034$, 95% CI [.254, .387]). Figure 9 shows the regression lines of the two genotypes on fixation time to the eyes along ASQ score. Descriptively, A-carriers show higher fixation times at lower ASQ than G-carriers, which decline with rising ASQ scores. G-carriers show no changes of fixation time along ASQ score, but the confidence of the regression lines overlap throughout the entire plot, visualising no significant effect. Thus, EH4.2 was not supported.

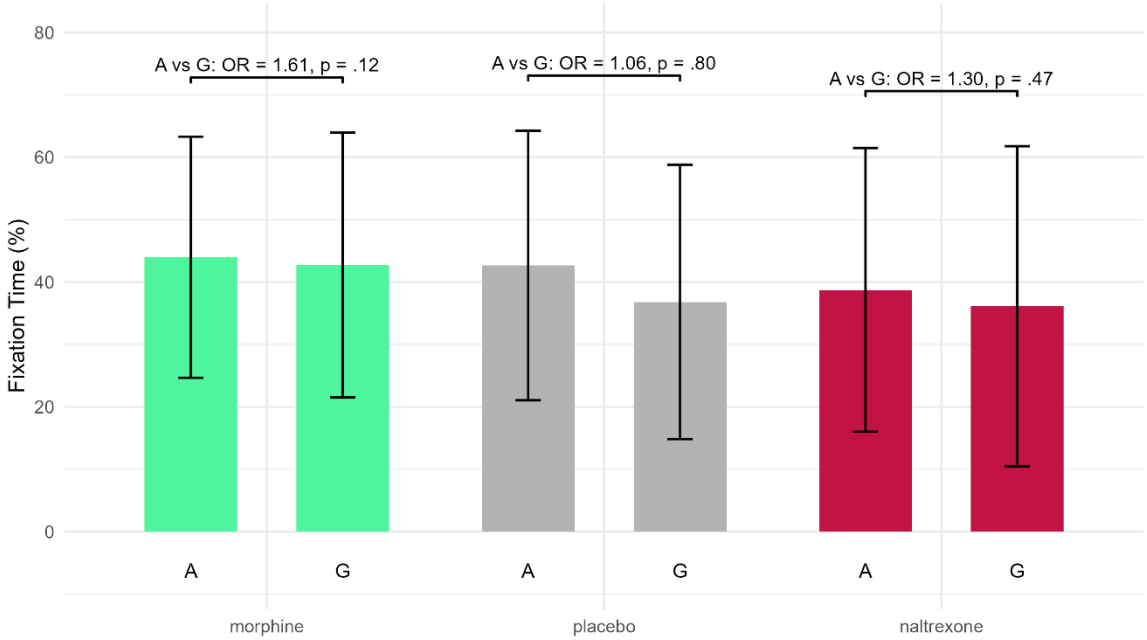
Figure 9. Predicted fixation across ASQ by genotype



6.5 Exploratory Hypothesis V

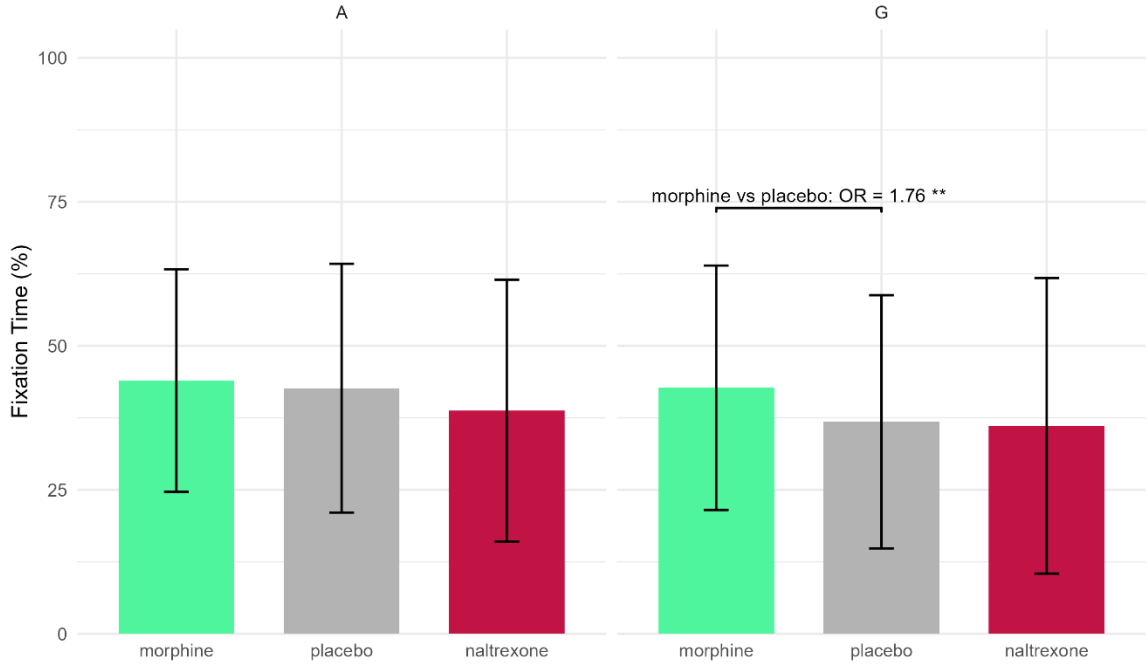
EH5.1 stated that morphine and genotype would interact, with G-carriers showing a bigger increase in eye-region fixation time stimulation via morphine, while EH5.2 stated that with naltrexone G-carriers would show greater inhibition compared to A-carriers. In model 4, the Drug × Genetics interaction was not significant, $\chi^2(2) = 2.30$, $p = .317$. Consistent with this, neither the morphine × Genetics interaction, $b = 0.422$, $SE = 0.284$, $z = 1.49$, $p = .137$, nor the naltrexone × Genetics interaction, $b = 0.217$, $SE = 0.437$, $z = 0.50$, $p = .619$, reached significance. Pairwise comparisons between genotype for each drug condition, plotted in Figure 10, showed no significant differences.

Figure 10. Genotype effects under morphine, naltrexone and placebo



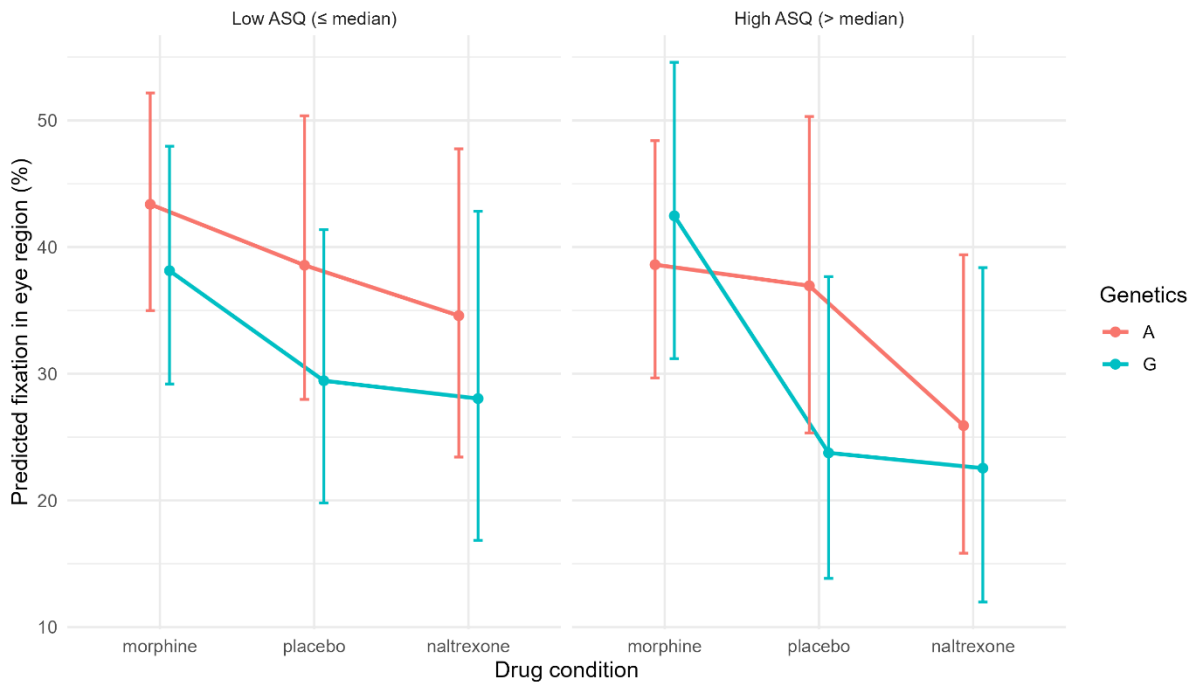
Descriptively, among G-allele carriers, morphine was associated with significantly greater eye-region fixation than placebo, OR = 1.76, $z = 2.74$, $p = .017$, whereas this difference was not significant among A/A homozygotes, OR = 1.15, $z = 0.74$, $p = .738$. However, because the overall interaction was non-significant, this pattern should not be interpreted as reliable evidence that G-allele carriers responded more strongly to morphine. Likewise, naltrexone did not significantly differ from placebo in either A/A homozygotes, OR = 0.73, $z = -1.10$, $p = .517$, or G-allele carriers, OR = 0.90, $z = -0.30$, $p = .950$. Thus, EH5.1 and EH5.2 were not supported.

Figure 11. Simple effects: Drug differences within genotype



The final exploratory hypothesis EH5.3 stated that the effects of μ-opioid manipulation and OPRM1 genotype on eye-region fixations would further vary as a function of autistic traits. In the full three-way interaction model, the Drug × Genetics × ASQ interaction was not significant, $\chi^2(2) = 1.63$, $p = .443$. Consistent with this, neither the morphine × Genetics × ASQ interaction, $b = 0.050$, $SE = 0.040$, $z = 1.26$, $p = .206$, nor the naltrexone × Genetics × ASQ interaction, $b = 0.029$, $SE = 0.059$, $z = 0.48$, $p = .628$, reached significance. In addition, the lower-order interactions Drug × Genetics, $\chi^2(2) = 2.49$, $p = .288$, Drug × ASQ, $\chi^2(2) = 1.06$, $p = .589$, and Genetics × ASQ, $\chi^2(1) = 0.39$, $p = .533$, were also non-significant. When calculating post-hoc contrasts between drug conditions for A-carriers and G-carriers individually, none were significant except morphine versus placebo in G carriers, OR = 1.76, z = -2.74, p = 0.006, 95% CI [1.17, 2.63]. Thus, EH5.3 was not supported, indicating no reliable evidence that the combined effects of drug condition and genotype on visual attention to the eye region differed according to ASQ scores.

Figure 12. Three-way-interaction: Drug x Genotype x ASQ (ASQ was median-split)



Descriptively, the plot suggests that morphine was associated with the highest predicted fixation on the eye region across both low and high ASQ groups, whereas naltrexone was associated with the lowest fixation levels. In the low ASQ group, A/A homozygotes showed consistently higher predicted eye fixations than G-allele carriers across all drug conditions, with both genotype groups showing a gradual decrease from morphine to placebo to naltrexone. In the high ASQ group, the pattern appeared less parallel: under morphine, G-allele carriers showed slightly higher predicted eye fixations than A/A homozygotes, but under placebo and naltrexone, A/A homozygotes again showed higher predicted values. Overall, the figure suggests possible differences in the pattern of drug effects across genotype and ASQ level, but these differences should be interpreted cautiously given the wide and overlapping confidence intervals.

7. Discussion

7.1 Findings

7.1.1 Drug effects – μ-opioid manipulation of gaze behaviour

One main point of discussion is the difference in drug effect results between the publication of Chelnokova et al. (2016) and this study. Comparing their reported drug contrasts, with those reported in the additional results in the appendix using a Linear Mixed Effects Model, and finally the preregistered methodology provides the possibility of dissecting the effects of individual methodological choices on the results.

For female face stimuli the original study had reported all contrasts as significant, with morphine showing the largest effects (M > N: t = 5.53***, M > P: t = 3.00**, P > N: t = 2.54*) for male face stimuli the morphine effect compared to placebo was not significant, while for naltrexone it was (M > N: t = 4.03***, P > N: t = 3.00*). The additional results using a Linear Mixed Effects Model with its main difference (apart from small differences between SPSS, that was used in the original study, and R) being the inclusion of drug as a random slope, showed a slight overall decrease in t-values (related to some variance being now attributed to the individual drug effects – random slope), with the naltrexone-placebo contrast being insignificant. All other contrasts matched the previous ones. Running the same model without random slopes brought the naltrexone effect to p = .07.

Compared to the Linear Mixed Effects Model using random slopes, the analysis in this study differs in only two regards. It uses a generalized linear mixed-effects model (GLMM), fitted using a beta distribution with a logit link function to model the fixation proportions and it reports the generalized results over both stimuli genders, although including it as a control variable. As was shown in the results the morphine effect was robust to these methodological changes in the complete dataset of 49 participants, while the naltrexone effect diminished. The additional dataset was likely underpowered to replicate the morphine effects. In the original dataset of 30 participants, the morphine contrasts were not significant, likely due to differences in the modelling approach compared to the original analysis. The effect of morphine was significant only in the complete dataset of 49

participants. In conclusion, the morphine effect was robust to the differences in analysis compared to Chelnokova et al. (2016), when adjusting sample size according to the increase in model complexity.

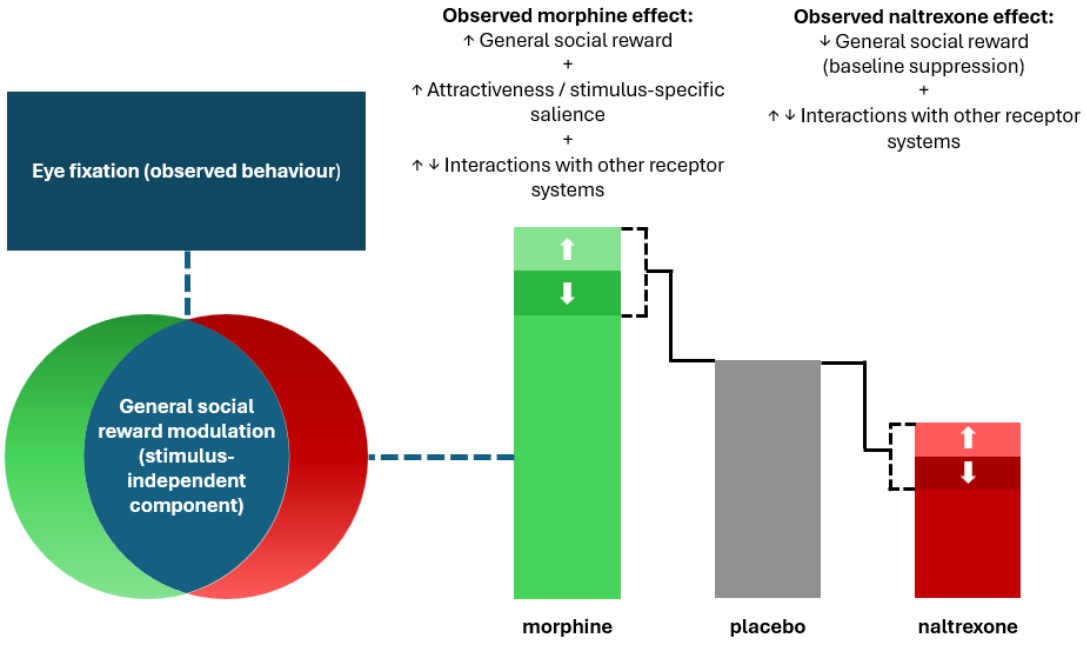
Morphine administration consistently influenced gaze allocation toward the eye region across analytical specifications, although the magnitude and statistical reliability of this effect depended on both model structure and sample composition. This suggests that μ-opioid agonism does exert measurable effects on attentional components of social perception, but that these effects are not invariant properties of the system. In contrast, naltrexone effects were comparatively fragile and diminished under more complex modelling, indicating that antagonist-driven reductions in social attention may not generalize as strongly across analytic choices or stimulus contexts.

Splitting the results by face gender, as was done in the paper, dealt with the biggest confounder of the effects of interest in a way that still enabled the reporting of significant stimulation (morphine) and inhibition (naltrexone) effects. However, to address a research question concerning generalized effects of the μ-opioid system on social reward processing, confounding effects of stimulus gender need to be accounted for within a unified model. Controlling for face gender resulted in a substantial reduction in explained variance of the drug effects, with the naltrexone effect in particular losing robustness. When stimulus gender is treated as a stratifying factor, more pronounced and apparently opposing drug effects emerge. When it is instead treated as a covariate in a generalized model, a substantial proportion of variance in drug effects is absorbed, and some previously significant contrasts are attenuated. This indicates that stimulus gender is not merely a nuisance variable but likely a meaningful moderator of opioid effects on social perception, at least for male participants.

It is worth discussing why morphine shows much stronger effects for female faces, whereas naltrexone does so for male faces. One possible explanation is that morphine, a μ-opioid receptor agonist, may amplify the rewarding and potentially attractiveness-related aspects of socially salient stimuli, which could be more strongly elicited by female faces in male participants. In contrast, naltrexone, an antagonist, may preferentially dampen more general social-reward processes that are less tied to attractiveness per se.

This pattern suggests that the observed drug effects may not reflect a single underlying mechanism, but rather a combination of partially distinct processes within the μ-opioid system. The effects observed under morphine may include both a general increase in social reward sensitivity and an additional amplification of stimulus-specific factors such as attractiveness, while naltrexone may primarily reduce a more baseline level of social motivation. These processes may also involve interactions with other receptor systems, further contributing to the observed dissociation. Thus, rather than interpreting each drug effect in isolation, the most informative signal may be the component that is consistent across both manipulations, the overlap of the morphine and naltrexone effect visualized in Figure 13, reflecting a general μ-opioid contribution to social reward processing independent of stimulus-specific influences.

Figure 13. Visualization of overlap hypothesis



A speculative interpretation is that morphine enhances the incentive salience ("wanting") of socially rewarding cues, whereas naltrexone reduces baseline hedonic tone or social motivation more broadly. The opioidergic system is implicated in both motivational ("wanting") and hedonic aspects ("liking") of reward processing. Within this framework, morphine may increase the motivational pull of socially salient stimuli, thereby enhancing gaze allocation to the eyes, whereas naltrexone may

dampen baseline social reward sensitivity, leading to reduced engagement. This distinction may explain why morphine effects appear more strongly tied to attractiveness, while naltrexone effects appear more generalized.

One could further hypothesize that the robust morphine effects—when stratified by stimulus gender—are largely driven by responses to female faces in male participants. Under this interpretation, the apparent general effect of μ-opioid stimulation on social attention may partly reflect an amplification of a more specific attentional bias toward attractive female faces. If so, inclusion of female participants might substantially alter or attenuate these effects. More specifically, this raises the possibility that the observed morphine effects would not generalize across the full 2×2 stimulus–participant matrix (male vs. female observers × male vs. female faces), but instead reflect a more restricted interaction pattern driven by male-specific attentional biases. This would challenge the interpretation of a generalized μ-opioid modulation of attention to the eye region.

Another important consideration is the role of participant characteristics and generalizability. While Chelnokova et al. (2016) limited recruitment to male participants to eliminate confounding hormonal fluctuations, the present findings suggest that this restriction may substantially limit generalizability. Given known sex differences in social perception and opioid system functioning, it is plausible that the interaction between drug and stimulus gender would differ in female participants. Evidence indicates that μ-opioid receptor availability and binding potential differ between males and females and are modulated by hormonal factors such as estradiol. In addition, females often show enhanced sensitivity to social cues, whereas male participants tend to show stronger attentional biases toward attractive female faces. Together, these findings suggest that the interaction between drug effects and stimulus gender is likely to differ substantially in female samples, challenging assumptions of straightforward generalizability across sexes.

Beyond the fact that results may only be generalizable to male populations, this study also shows that the effects of μ-opioid manipulation on attention to the eyes are smaller than one might expect from the results of Chelnokova et al. (2016).

7.1.2 Autistic traits and attention to the eyes

Contrary to Hypothesis 2, no significant association was observed between autistic traits and attention to the eye region. This finding contrasts with prior literature linking higher autistic traits to reduced social motivation and decreased attention to socially salient facial features, particularly the eyes (Chevallier et al., 2012; Frazier et al., 2017). One possible explanation is that the present study assessed subclinical variation within a neurotypical sample, whereas many previous findings are based on comparisons involving clinically diagnosed individuals. It is therefore plausible that the relationship between autistic traits and gaze behaviour is non-linear, with stronger effects emerging only at clinically relevant levels of symptom severity.

Additionally, the inclusion of pharmacological manipulation and multiple covariates may have further attenuated the contribution of trait-level predictors such as ASQ. Taken together, these findings suggest that while autistic traits are theoretically linked to social attention, their behavioural manifestation in gaze patterns may depend on sample characteristics, task context, and measurement sensitivity.

7.1.3 Genotype null findings

Although null findings were consistent in all parts of the analysis that involved genotype, the large difference in distribution in the clinical sample of Hamilton (2020) and the general population does suggest a link between ASC and the OPRM1 polymorphism and descriptively there seem to be differences in drug effects by genotype. For the ASQ analysis it is highly likely that these differences in genetic distribution do not carry over to sub-clinical variations in autistic traits. However, null findings do not mean absence of true effects. Although the original a priori power analysis may have been adequate for the effect size assumed at the planning stage, that assumption was likely optimistic for single-variant behavioural associations. Complex behavioural phenotypes are now understood to be highly polygenic, and individual common variants typically account for only a very small proportion of phenotypic variance; accordingly, candidate-gene findings in behavioural science have often been underpowered and difficult to replicate (Chabris et al., 2013; Munafò, 2011). This issue is especially relevant here because genotype was tested as a between-subject factor within a relatively complex

mixed-effects framework: in multilevel models, power for higher-level predictors depends primarily on the number of participants rather than the number of repeated observations, and substantial random-slope heterogeneity can further reduce precision (Snijders, 2005). Thus, the null genotype findings in the present sample of 49 participants should be interpreted cautiously, as they may reflect limited sensitivity to detect subtle genotype-related effects rather than true absence of such effects. The same caution applies even more strongly to Drug × Genetics effects, because interaction tests generally require markedly larger samples than comparable main effects. For future work, a more conservative strategy could be to base sample-size planning on simulation-based power analyses that preserve the observed genotype imbalance, so the group sizes of the categorical Genotype variable and full random-effects structure of the model rather than relying on simplified analytic approximations (Thomas, 2010;; Kumle et al., 2021).

A short simulation-based power analysis was conducted to evaluate the sensitivity of the present modelling approach for detecting genotype-related effects under realistic design conditions. The simulation parameters were derived from Model 4, including the observed fixed effects, the full random-effects structure with random intercepts and drug slopes, and their estimated variance–covariance matrix. The simulated design closely matched the empirical study, assuming 49 participants with an imbalanced genotype distribution (approximately 27 A/A and 22 A/G carriers) and 480 repeated observations per participant across drug conditions. Outcome data were generated from a beta distribution with a logit link (precision parameter $\varphi = 4.5$), reflecting the proportional nature of the dependent variable. Power was estimated using likelihood ratio tests comparing nested models for both the main effect of genotype and the Drug × Genetics interaction across varying sample sizes. To provide a conservative benchmark, small effect sizes were specified as odds ratios of 1.10 (i.e., log-odds ≈ 0.095), consistent with expectations for single-variant behavioral associations (Chabris et al., 2013; Munafò, 2011). Results indicated very low power to detect such small genotype effects at the current sample size (N = 49; power ≈ .06–.10), with only modest increases even at substantially larger sample sizes (e.g., power < .35 at N = 400). These findings suggest that the present study was substantially underpowered to detect realistic genotype effects, particularly interactions, and that future studies would

require considerably larger samples or alternative designs (e.g., extreme-group sampling) to achieve adequate statistical sensitivity.

7.2 Overall strengths and limitations

The present study is characterized by a combination of methodological strengths and important limitations that should be considered when interpreting the findings. A key limitation lies in the reliance on self-reported subclinical autistic traits. While dimensional approaches such as the ASQ provide valuable insight into variation within the general population, they may not fully capture the complexity and heterogeneity of clinically diagnosed autism spectrum conditions. Consequently, the absence of robust associations between autistic traits and gaze behaviour in this study does not necessarily generalize to clinical populations, where effects tend to be more pronounced and consistent.

At the same time, the use of a preregistered and systematic analysis pipeline represents a major strength. Although preregistration occurred after data collection and dataset merging, it was completed prior to any analyses on the full dataset, thereby substantially reducing researcher degrees of freedom in model specification, hypothesis testing, and reporting. The preregistration clearly defined research questions, hypotheses, statistical models, inclusion criteria, and planned post hoc tests, as well as procedures for handling model convergence and assumption violations. This level of specification mitigates common reproducibility issues such as undisclosed analytic flexibility, selective reporting, and hypothesizing after results are known (HARKing). Furthermore, by explicitly distinguishing confirmatory and exploratory analyses, the study increases transparency in the interpretation of findings.

However, preregistration at this stage cannot fully eliminate all sources of bias, for example it has no effect on any possible biases in the data collection phase of the study. Furthermore, as the original dataset had been previously analysed and published, prior knowledge of the data structure and effects may have influenced expectations and analytic decisions. Thus, while the preregistration substantially strengthens the credibility and transparency of the findings, it does not fully equate to a prospective preregistration conducted prior to data collection.

Future research could further improve sensitivity and generalizability by adopting alternative designs. Extreme-group or clinical designs may enhance the ability to detect associations with autistic

traits by increasing variance and effect sizes. Including clinically diagnosed individuals would allow for a more direct test of theories linking social motivation deficits to gaze behaviour.

For genetic analyses, the present results suggest that single genetic variants may not be a practically feasible target for this type of experimental design, with simulation-based power analysis showing a lack of power even for very large sample sizes (e.g., power remaining < .35 at N = 400), which would be challenging to achieve for a three drug within-subject design.

8. Conclusion

The thesis set out to examine whether pharmacological manipulation of the μ-opioid system modulates visual attention to the eye region and whether such effects interact with individual differences in autistic traits and genetic variation. Given the central role of the eyes as socially salient facial features, such modulation was interpreted as reflecting changes in social reward processing.

Across analyses, μ-opioid modulation of gaze behaviour was evident but not uniform. Morphine administration showed the most consistent effects, increasing attention to the eye region, whereas naltrexone effects were less robust and diminished under more stringent modelling approaches. These findings suggest that μ-opioid agonism can influence attentional components of social perception, but that these effects are sensitive to context and analytic specification rather than reflecting stable, invariant properties of the system.

Taken together, the results point toward a nuanced account in which μ-opioid influences on social attention arise from the interaction of multiple processes rather than a single unified mechanism. Opioid modulation may differentially affect motivational and perceptual components of social engagement, such that the impact on gaze behaviour depends on the salience and value of the stimulus as well as characteristics of the observer. In this view, opioid signalling does not globally enhance or suppress social interest but operates in a context-dependent manner.

The absence of robust associations between autistic traits and gaze behaviour further refines this interpretation. Within the present non-clinical sample, variation in self-reported autistic traits did not translate into measurable differences in attention to the eye region. This suggests that subclinical variation may be insufficient to produce detectable differences in gaze allocation under the current

task conditions, consistent with the idea that stronger behavioural effects emerge primarily at clinically relevant levels.

Similarly, no reliable evidence for genetic moderation was observed. While this may reflect limited statistical sensitivity to detect small effects, the findings are also consistent with broader evidence that complex social behaviours are unlikely to be explained by single genetic variants in isolation.

Overall, the present findings support a more context-sensitive understanding of μ-opioid involvement in social behaviour. Rather than reflecting a general mechanism regulating social attention, opioid effects appear to be shaped by the interaction of pharmacological manipulation, stimulus characteristics, and individual differences. This highlights the importance of considering both methodological and contextual factors when interpreting pharmacological influences on social cognition.

References

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

Barr, C. S., Schwandt, M. L., Lindell, S. G., Higley, J. D., Maestripieri, D., Goldman, D., Suomi, S. J., & Heilig, M. (2008). Variation at the mu-opioid receptor gene (OPRM1) influences attachment behavior in infant primates. *Proceedings of the National Academy of Sciences of the United States of America, 105*(13), 5277–5281. https://doi.org/10.1073/pnas.0710225105

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J. & Clubley, E. The Autism-Spectrum Quotient (AQ): Evidence from Asperger Syndrome/High-Functioning Autism, Malesand Females, Scientists and Mathematicians. *J. Autism Dev. Disord. 31*, 5–17 (2001).

Baum, S. H., Stevenson, R. A., & Wallace, M. T. (2015). Behavioral, perceptual, and neural alterations in sensory and multisensory function in autism spectrum disorder. Progress in Neurobiology, 134, 140-160. http://dx.doi.org/10.1016/j.pneurobio.2015.09.007

Berridge, K. C., & Kringelbach, M. L. (2015). Pleasure Systems in the Brain. Neuron, 86(3), 646–664. https://doi.org/10.1016/j.neuron.2015.02.018 Berridge, K. C., Robinson, T. E., & Aldridge, J. W. (2009). Dissecting components of reward: 'Liking', 'wanting', and learning. Current Opinion in Pharmacology, 9(1), 65–73. https://doi.org/10.1016/j.coph.2008.12.014

Bolis, D., & Schilbach, L. (2018). Observing and participating in social interactions: Action perception and action control across the autistic spectrum. *Developmental Cognitive Neuroscience*, *29*, 168–175. https://doi.org/10.1016/j.dcn.2017.01.009

Bond, C., LaForge, K. S., Tian, M., Melia, D., Zhang, S., Borg, L., Gong, J., Schluger, J., Strong, J. A., Leal, S. M., Tischfield, J. A., Kreek, M. J., & Yu, L. (1998). Single-nucleotide polymorphism in the human mu opioid receptor gene alters β-endorphin binding and activity: Possible implications for opiate addiction. *Proceedings of the National Academy of Sciences*, *95*(16), 9608–9613. https://doi.org/10.1073/pnas.95.16.9608

Bottini, S. (2018). Social reward processing in individuals with autism spectrum disorder: A systematic review of the social motivation hypothesis. *Research in Autism Spectrum Disorders*, *45*, 9–26. https://doi.org/10.1016/j.rasd.2017.10.001

Briand, L. A., Hilario, M., Dow, H. C., Brodkin, E. S., Blendy, J. A., & Berton, O. (2015). Mouse model of OPRM1 (A118G) polymorphism increases sociability and dominance and confers resilience to social defeat. *Journal of Neuroscience, 35*(8), 3582–3590. https://doi.org/10.1523/JNEUROSCI.4685-14.2015

Chabris, C. F., Lee, J. J., Cesarini, D., Benjamin, D. J., & Laibson, D. I. (2015). The Fourth Law of Behavior Genetics. *Current Directions in Psychological Science*, *24*(4), 304–312. https://doi.org/10.1177/0963721415580430

Chelnokova, O., Laeng, B., Eikemo, M., Riegels, J., Løseth, G., Maurud, H., Willoch, F., & Leknes, S. (2014). Rewards of beauty: The opioid system mediates social motivation in humans. *Molecular Psychiatry, 19*(7), 746–747. https://doi.org/10.1038/mp.2014.1

Chelnokova, O., Laeng, B., Løseth, G., Eikemo, M., Willoch, F., & Leknes, S. (2016). The μ-opioid system promotes visual attention to faces and eyes. *Social Cognitive and Affective Neuroscience, 11*(12), 1902–1909. https://doi.org/10.1093/scan/nsw116

Chetcuti, L., Hardan, A. Y., Spackman, E., Loth, E., McPartland, J. C., Frazier, T. W., Youngstrom, E. A., & Uljarevic, M. (2025). Parsing the heterogeneity of social motivation in autism. *Journal of Child Psychology and Psychiatry*, *66*(9), 1376–1389. https://doi.org/10.1111/jcpp.14147

Chevallier, C., Kohls, G., Troiani, V., Brodkin, E. S., & Schultz, R. T. (2012). The social motivation theory of autism. *Trends in Cognitive Sciences, 16*(4), 231–239. https://doi.org/10.1016/j.tics.2012.02.007

Chita-Tegmark, M. (2016). Attention allocation in ASD: A review and meta-analysis of eye-tracking studies. *Review Journal of Autism and Developmental Disorders, 3*(3), 209–223. https://doi.org/10.1007/s40489-016-0077-x

Conway, C. A., Jones, B. C., Debruine, L. M., Little, A. C., Hay, J., Welling, L. L. M., … Feinberg, D. R. (2008). Integrating physical and social cues when forming face preferences: Differences among

low and high-anxiety individuals. *Social Neuroscience*, *3*(1), 89–95. https://doi.org/10.1080/17470910701676145

Copeland, W. E., Sun, H., Costello, E. J., Angold, A., Heilig, M. A., & Barr, C. S. (2011). Child μ-opioid receptor gene variant influences parent–child relations. *Neuropsychopharmacology, 36*(6), 1165–1170. https://doi.org/10.1038/npp.2010.251

Crompton, C. J., Ropar, D., Evans-Williams, C. V., Flynn, E. G., & Fletcher-Watson, S. (2020). Autistic peer-to-peer information transfer is highly effective. *Autism: The International Journal of Research and Practice*, *24*(7), 1704–1712. https://doi.org/10.1177/1362361320919286

Dalton, K. M., Nacewicz, B. M., Johnstone, T., Schaefer, H. S., Gernsbacher, M. A., Goldsmith H. H., Alexander, A. L., & Davidson, R. J. (2005). Gaze fixation and the neural circuitry of face processing in autism. Nat Neurosci, 8(4), 519-526. 48 https://doi.org/10.1038/nn1421

Dawson, G., Webb, S. J., & McPartland, J. (2005). Understanding the nature of face processing impairment in autism: Insights from behavioral and electrophysiological studies. *Developmental Neuropsychology, 27*(3), 403–424. https://doi.org/10.1207/s15326942dn2703_6

Dimitrov, M., Wong, N. M. L., Leaman, S., França, L. G. S., Valasakis, I., He, J., Lythgoe, D. J., Findon, J. L., Wichers, R. H., Stoencheva, V., Robertson, D. M., Blainey, S., Ivin, G., Holiga, Š., Tricklebank, M. D., Batalle, D., Murphy, D. G. M., McAlonan, G. M., & Daly, E. (2025). μ-Opioid modulation of sensorimotor functional connectivity in autism: Insights from a pharmacological neuroimaging investigation using tianeptine. *medRxiv*. https://doi.org/10.1101/2025.03.12.25323848

Emery, N. J. (2000). The eyes have it: The neuroethology, function and evolution of social gaze. *Neuroscience & Biobehavioral Reviews, 24*(6), 581–604. https://doi.org/10.1016/S0149-7634(00)00025-7

Fields, H. L. (2004). State-dependent opioid control of pain. *Nature Reviews Neuroscience, 5*(7), 565–575. https://doi.org/10.1038/nrn1431

Frazier, T. W., Strauss, M., Klingemier, E. W., Zetzer, E. E., Hardan, A. Y., Eng, C., & Youngstrom, E. A. (2017). A meta-analysis of gaze differences to social and nonsocial information between

individuals with and without autism. *Journal of the American Academy of Child & Adolescent Psychiatry, 56*(7), 546–555. https://doi.org/10.1016/j.jaac.2017.05.005

Genovese, A., & Butler, M. G. (2020). Clinical Assessment, Genetics, and Treatment Approaches in Autism Spectrum Disorder (ASD). International Journal of Molecular Sciences, 21, 4726. https://doi.org/10.3390/ijms21134726

Grelotti, D. J., Gauthier, I., & Schultz, R. T. (2002). Social interest and the development of cortical face specialization: What autism teaches us about face processing. Developmental Psychobiology, 40(3), 213–225. https://doi.org/10.1002/dev.10028

Grzadzinski, R., Huerta, M., & Lord, C. (2013). DSM-5 and autism spectrum disorders (ASDs): An opportunity for identifying ASD subtypes. *Molecular Autism, 4*(1), Article 1. https://doi.org/10.1186/2040-2392-4-12

Haffey, A., Hsu, C.-T., & Chakrabarti, B. (2025). Autistic traits modulate neural and behavioral responses to social versus nonsocial rewards. *Personality Neuroscience, 8*, e4. https://doi.org/10.1017/pen.2025.10003

Hamilton, K. 2020. The biological bases of social deficits: the roles of social motivation, theory of mind, and selected genotypes (OPRM1, 5-HTTLPR) in autism spectrum disorder. Faculty of Humanities, Department of Psychology. http://hdl.handle.net/11427/32659

Hanley, M., Riby, D. M., Carty, C., Melaugh McAteer, A., Kennedy, A., & McPhillips, M. (2015). The use of eye-tracking to explore social difficulties in cognitively able students with autism spectrum disorder: A pilot investigation. Autism, 19(7), 868-873. https://doi.org/10.1177/1362361315580767

Hernandez, N., et al. (2009). Exploration of core features of a human face by healthy and autistic adults analyzed by visual scanning. *Neuropsychologia, 47*, 1004–1012.

Hikosaka, O., Nakamura, K., & Nakahara, H. (2006). Basal ganglia orient eyes to reward. *Journal of Neurophysiology, 95*(2), 567–584. https://doi.org/10.1152/jn.00458.2005

Hsu, D. T., Sanford, B. J., Meyers, K. K., Love, T. M., Hazlett, K. E., Wang, H., Ni, L., Walker, S. J., Mickey, B. J., Korycinski, S. T., Koeppe, R. A., Crocker, J. K., Langenecker, S. A., & Zubieta, J.-K. (2013). Response of the μ-opioid system to social rejection and acceptance. *Molecular Psychiatry, 18*(11), 1211–1217. https://doi.org/10.1038/mp.2013.96

Hull, L., Petrides, K. V., Allison, C., Smith, P., Baron-Cohen, S., Lai, M.-C., & Mandy, W. (2017). "Putting on My Best Normal": Social Camouflaging in Adults with Autism Spectrum Conditions. J Autism Dev Disorder, 47, 2519-2534. https://doi.org/10.1007/s10803-017-3166-5

Itier, R. J., & Batty, M. (2009). Neural bases of eye and gaze processing: The core of social cognition. *Neuroscience & Biobehavioral Reviews*, *33*(6), 843–863. https://doi.org/10.1016/j.neubiorev.2009.02.004

Jaswal, V. K., & Akhtar, N. (2018). Being versus appearing socially uninterested: Challenging assumptions about social motivation in autism. *The Behavioral and Brain Sciences*, *42*, e82. https://doi.org/10.1017/S0140525X18001826

Jones, W., & Klin, A. (2013). Attention to Eyes is Present But in Decline in 2–6 Month-Olds 53 Later Diagnosed with Autism. *Nature*, *504*(7480), 427-431. https://doi.org/10.1038/nature12715

Joseph, R. M., Tager-Flusberg, H., & Lord, C. (2002). Cognitive profiles and social-communicative functioning in children with autism spectrum disorder. *Journal of Child Psychology and Psychiatry, 43*(6), 807–821. https://doi.org/10.1111/1469-7610.00092

Klin, A., Jones, W., Schultz, R., Volkmar, F., & Cohen, D. (2002). Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. Arch Gen Psychiatry, 59(9), 809-816. https://doi.org/10.1001/archpsyc.59.9.809

Klin, A., Micheletti, M., Klaiman, C., Shultz, S., Constantino, J. N., & Jones, W. (2020). Affording autism an early brain development re-definition. *Dev Psychopathol*, *32*(4), 1175-89. https://doi.org/10.1017/S0954579420000802

Kohls, G., Schulte-Rüther, M., Nehrkorn, B., Müller, K., Fink, G. R., Kamp-Becker, I., Herpertz-Dahlmann, B., Schultz, R. T., & Konrad, K. (2013). Reward system dysfunction in autism

spectrum disorders. *Social Cognitive and Affective Neuroscience*, *8*(5), 565–572. https://doi.org/10.1093/scan/nss033

Kumle, L., Võ, M. L.-H., & Draschkow, D. (2021). Estimating power in (generalized) linear mixed models: An open introduction and tutorial in R. *Behavior Research Methods*, *53*(6), 2528–2543. https://doi.org/10.3758/s13428-021-01546-0

LoParo, D., & Waldman, I. D. (2015). The oxytocin receptor gene (OXTR) is associated with autism spectrum disorder: A meta-analysis. *Molecular Psychiatry, 20*(5), 640–646. https://doi.org/10.1038/mp.2014.77

Løseth, G., Trøstheim, M., & Leknes, S. (2024). Endogenous mu-opioid modulation of social connection in humans: A systematic review and meta-analysis. *Translational Psychiatry, 14*(1), 379. https://doi.org/10.1038/s41398-024-03088-3

Manninen, S., Tuominen, L., Dunbar, R. I. M., Karjalainen, T., Hirvonen, J., Arponen, E., Hari, R., Jääskeläinen, I. P., Sams, M., & Nummenmaa, L. (2017). Social laughter triggers endogenous opioid release in humans. *Journal of Neuroscience, 37*(25), 6125–6131. https://doi.org/10.1523/JNEUROSCI.0688-16.2017

Marshall, C. R., Noor, A., Vincent, J. B., Lionel, A. C., Feuk, L., Skaug, J., Shago, M., Moessner, R., Pinto, D., Ren, Y., Thiruvahindrapduram, B., Fiebig, A., Schreiber, S., Friedman, J., Ketelaars, C. E.J., Vos, Y. J., Ficicioglu, C., Kirkpatrick, S., Nicolson, 57 R., ... Scherer, S. W. (2008). Structural variation of chromosomes in autism spectrum disorder. *AJHG*, *82*(2), 477–488. https://doi.org/10.1016/j.ajhg.2007.12.009

Maunsell, J. H. R. (2004). Neuronal representations of cognitive state: Reward or attention? *Trends in Cognitive Sciences*, *8*(6), 261–265. https://doi.org/10.1016/j.tics.2004.04.003

Milton, D. E. M. (2012). On the ontological status of autism: The 'double empathy problem'. *Disability & Society*, *27*(6), 883–887. https://doi.org/10.1080/09687599.2012.710008

Moles, A., Kieffer, B. L., & D'Amato, F. R. (2004). Deficit in attachment behavior in mice lacking the mu-opioid receptor gene. *Science, 304*(5679), 1983–1986. https://doi.org/10.1126/science.1095943

Munafò, M. R., & Flint, J. (2011). Dissecting the genetic architecture of human personality. *Trends in Cognitive Sciences, Special Issue: The Genetics of Cognition*, *15*(9), 395–400. https://doi.org/10.1016/j.tics.2011.07.007

Mundy, P., & Newell, L. (2007). Attention, Joint Attention, and Social Cognition. *Current Directions in Psychological Science*, *16*(5), 269–274. https://doi.org/10.1111/j.1467-8721.2007.00518.x

Neumann, D., Spezio, M. L., Piven, J., Adolphs, R. (2006). Looking you in the mouth: abnormal gaze in autism resulting from impaired top-down modulation of visual attention. Soc Cogn Affect Neurosci, 1(3), 194-202. https://doi.org/10.1093/scan/nsl030

Noris, B., Nadel, J., Barker, M., Hadjikhani, N., & Billard, A. (2012). Investigating gaze of children with ASD in naturalistic settings. PLoS One, 7(9), e44144. https://doi.org/10.1371/journal.pone.0044144

Nummenmaa, L., Tuominen, L., Dunbar, R. I. M., Hirvonen, J., Manninen, S., Arponen, E., Machin, A. J., Hari, R., Jääskeläinen, I. P., & Sams, M. (2016). Social touch modulates endogenous μ-opioid system activity in humans. *NeuroImage, 138*, 242–247. https://doi.org/10.1016/j.neuroimage.2016.05.063

Panksepp, J. (1979). A neurochemical theory of autism. *Trends in Neurosciences*, 2, 174–177.

Peciña, S. (2008). Opioid reward "liking" and "wanting" in the nucleus accumbens. *Physiology & Behavior, 94*(5), 675–680. https://doi.org/10.1016/j.physbeh.2008.04.006

Pellissier, L. P., Gandía, J., Laboute, T., Becker, J. A. J., & Le Merrer, J. (2018). μ opioid receptor, social behaviour and autism spectrum disorder: Reward matters. *British Journal of Pharmacology, 175*(14), 2750–2769. https://doi.org/10.1111/bph.13808

Persson, M. E., Sundman, A.-S., Halldén, L.-L., Trottier, A. J., & Jensen, P. (2018). Sociality genes are associated with human-directed social behaviour in golden and Labrador retriever dogs. *PeerJ, 6*, e5889. https://doi.org/10.7717/peerj.5889

Proverbio, A. M., Riva, F., Martin, E., & Zani, A. (2010). Sex differences in facial emotion recognition. *Neuropsychologia, 48*(11), 3552–3562. https://doi.org/10.1016/j.neuropsychologia.2010.07.024

Ray, L. A., & Hutchison, K. E. (2004). A polymorphism of the μ-opioid receptor gene (OPRM1) and sensitivity to the effects of alcohol in humans. *Alcoholism: Clinical and Experimental Research, 28*(12), 1789–1795. https://doi.org/10.1097/01.ALC.0000148114.34000.B9

Roy, A., Roy, M., Deb, S., Unwin, G., & Roy, A. (2015). Are opioid antagonists effective in attenuating the core symptoms of autism spectrum conditions in children: A systematic review. *Journal of Intellectual Disability Research, 59*(4), 293–306. https://doi.org/10.1111/jir.12122

Rupp, H. A., & Wallen, K. (2009). Sex differences in viewing sexual stimuli: An eye-tracking study in men and women. *Hormones and Behavior, 55*(4), 580–589. https://doi.org/10.1016/j.yhbeh.2009.03.019

Rylaarsdam, L., & Guemez-Gamboa, A. (2019). Genetic Causes and Modifiers of Autism Spectrum Disorder. Front. Cell. Neurosci., 13, 385. https://doi.org/10.3389/fncel.2019.00385

Schilbach, L., Timmermans, B., Reddy, V., Costall, A., Bente, G., Schlicht, T., & Vogeley, K. (2013). Toward a second-person neuroscience. *Behavioral and Brain Sciences, 36*(4), 393–414. https://doi.org/10.1017/S0140525X12000660

Schultz, R. T. (2005). Developmental deficits in social perception in autism: The role of the amygdala and fusiform face area. *International Journal of Developmental Neuroscience, 23*(2–3), 125–141. https://doi.org/10.1016/j.ijdevneu.2004.12.012

Schultz, W. (2006). Behavioral theories and the neurophysiology of reward. *Annual Review of Psychology*, *57*, 87–115. https://doi.org/10.1146/annurev.psych.56.091103.070229

Scott-Van Zeeland, A. A., Dapretto, M., Ghahremani, D. G., Poldrack, R. A., & Bookheimer, S. Y. (2010). Reward processing in autism. *Autism Research*, *3*(2), 53–67. https://doi.org/10.1002/aur.122

Smith, Y. R., Zubieta, J.-K., del Carmen, M. G., Dannals, R. F., Ravert, H. T., Zacur, H. A., & Frost, J. J. (1998). Brain opioid receptor measurements by positron emission tomography in normal cycling women: Relationship to luteinizing hormone pulsatility and gonadal steroid hormones.

Journal of Clinical Endocrinology & Metabolism, 83(12), 4498–4505. https://doi.org/10.1210/jcem.83.12.5315

Snijders, T. A. B., & Bosker, R. J. (2012). *Multilevel analysis: An introduction to basic and advanced multilevel modeling* (2nd ed.). SAGE Publications.

Speer, L. L., Cook, A. E., McMahon, W. M., & Clark, E. (2007). Face processing in children with autism: Effects of stimulus contents and type. Autism, 11(3), 265-277. https://doi.org/10.1177/1362361307076925

Stallworthy, I. C., Berry, D., Davis, S., Wolff, J. J., Burrows, C. A., Swanson, M. R., Grzadzinski, R. L., Botteron, K., Dager, S. R., Estes, A. M., Schultz, R. T., Piven, J., Elison, J. T., Pruett Jr., J. R., Marrus, N., & Network, for T. I. (2023). Quantifying latent social motivation and its associations with joint attention and language in infants at high and low likelihood for autism spectrum disorder. *Developmental Science*, *26*(3), e13336. https://doi.org/10.1111/desc.13336

Su, P. L., Rogers, S. J., Estes, A., & Yoder, P. (2021). The role of early social motivation in explaining variability in functional language in toddlers with autism spectrum disorder. *Autism*, *25*(1), 244–257. https://doi.org/10.1177/1362361320953260

Tanaka, J. W., & Sung, A. (2016). The “eye avoidance” hypothesis of autism face processing. *Journal of Autism and Developmental Disorders, 46*(5), 1538–1552. https://doi.org/10.1007/s10803-013-1976-7

Thomas, D. (2010). Gene–environment-wide association studies: Emerging approaches. *Nature Reviews Genetics*, *11*(4), 259–272. https://doi.org/10.1038/nrg2764

Trevisan, D. A., Roberts, N., Lin, C. & Birmingham, E. (2017). How do adults and teens with self-declared Autism Spectrum Disorder experience eye contact? A qualitative analysis of first-hand accounts. *PLOS ONE*, *12*, e0188446.

Troisi, A., Frazzetto, G., Carola, V., Di Lorenzo, G., Coviello, M., D’Amato, F. R., Moles, A., Siracusano, A., & Gross, C. (2011). Social hedonic capacity is associated with the A118G polymorphism of the mu-opioid receptor gene (OPRM1) in adult healthy volunteers and

psychiatric patients. *Social Neuroscience, 6*(1), 88–97. https://doi.org/10.1080/17470919.2010.482786

Trøstheim, M., Eikemo, M., Haaker, J., Frost, J. J., & Leknes, S. (2022). *Opioid Antagonism in Humans: A Primer on Optimal Dose and Timing for Central Mu-Opioid Receptor Blockade* (S. 2022.02.25.481943). bioRxiv. https://doi.org/10.1101/2022.02.25.481943

Tschida, J. E., & Yerys, B. E. (2021). A Systematic Review of the Positive Valence System in Autism Spectrum Disorder. *Neuropsychology Review*, *31*(1), 58–88. https://doi.org/10.1007/s11065-020-09459-z

Preller, K. H., Herdener, M., Schilbach, L., Stämpfli, P., Hulka, L. M., Vonmoos, M., Ingold, N., Vogeley, K., Tobler, P. N., Seifritz, E., & Quednow, B. B. (2014). Functional changes of the reward system underlie blunted response to social gaze in cocaine users. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(7), 2842–2847. https://doi.org/10.1073/pnas.1317090111

Wardle, M. C., Bershad, A. K., & de Wit, H. (2016). Naltrexone alters the processing of social and emotional stimuli in healthy adults. *Social Neuroscience*, *11*(6), 579–591. https://doi.org/10.1080/17470919.2015.1136355

Way, B. M., Taylor, S. E., & Eisenberger, N. I. (2009). Variation in the mu-opioid receptor gene (OPRM1) is associated with dispositional and neural sensitivity to social rejection. *Proceedings of the National Academy of Sciences of the United States of America, 106*(35), 15079–15084. https://doi.org/10.1073/pnas.0812612106

World Health Organization. (2019). *International classification of diseases for mortality and morbidity statistics (11th revision)*. https://icd.who.int/

World Health Organization. (1992). *The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines*. https://apps.who.int/iris/handle/10665/37958

Yang, C., Wang, X.-K., Ma, S.-Z., Lee, N. Y., Zhang, Q.-R., Dong, W.-Q., Zang, Y.-F., & Yuan, L.-X. (2024). Abnormal functional connectivity of the reward network is associated with social communication impairments in autism spectrum disorder: A large-scale multi-site resting-state

fMRI study. *Journal of Affective Disorders*, *347*, 608–618.

https://doi.org/10.1016/j.jad.2023.12.013

Tables

Figures

Appendix

Figure 14. Planned pairwise drug contrasts of linear mixed effects model for all three datasets

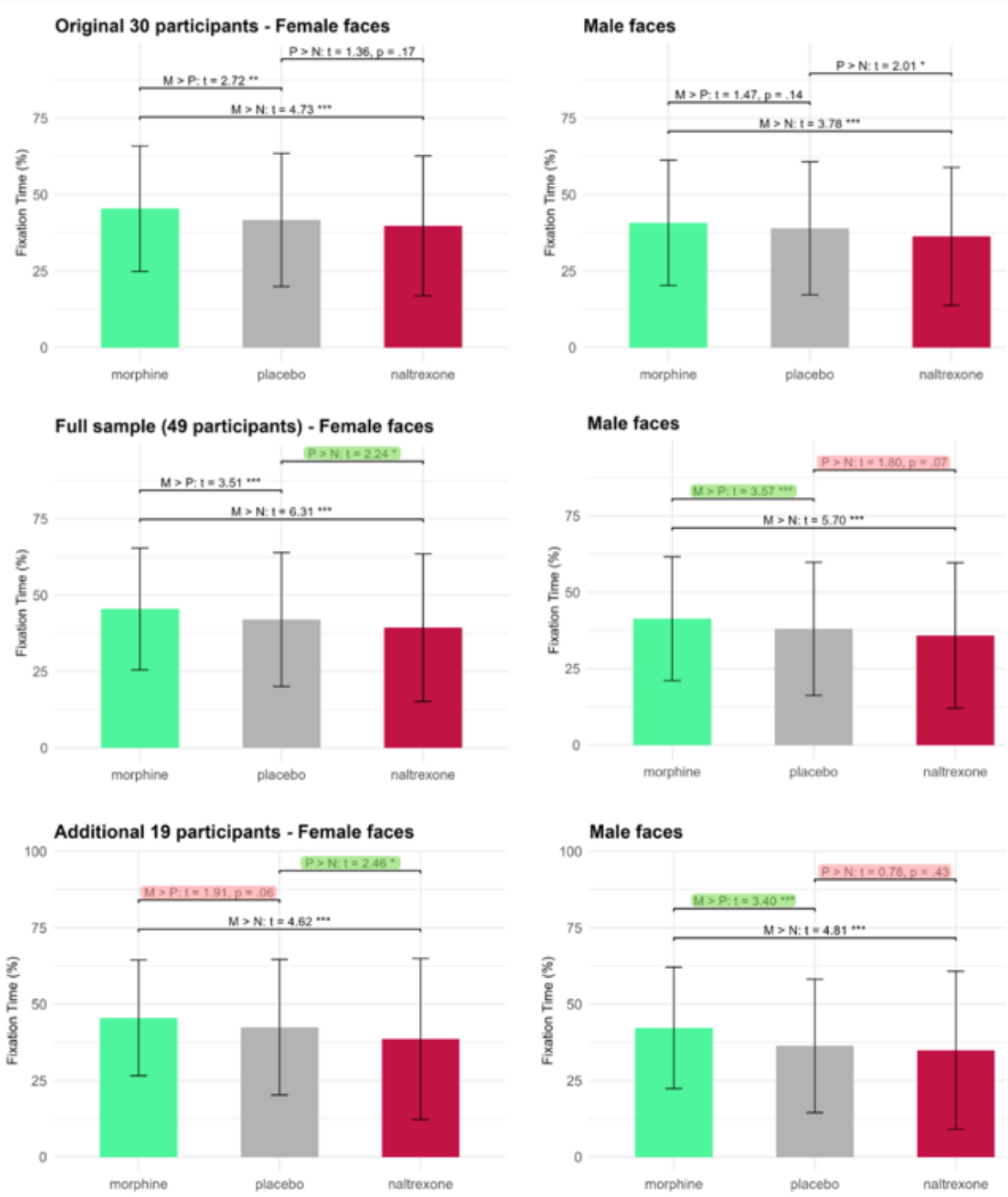


Figure 14 provides additional results for comparison with the original publication. The bar plots depict mean fixation proportions (± SD) to the eye region (AOI: eye_brow) across drug conditions, separately for female and male face stimuli, with inferential statistics derived from linear mixed-

effects models. For each dataset (original, additional, and full sample), fixation time percentages were analysed using a linear mixed-effects model (fit with maximum likelihood) including fixed effects of AOI, Drug (morphine, placebo, naltrexone), Gaze2, and AttrLevel, as well as their interactions, while controlling for StimOrder, Imagelist, and Session. Random intercepts and random slopes for Drug were specified for participants. Planned pairwise contrasts were computed using estimated marginal means at the eye region, comparing morphine vs. naltrexone (M > N), morphine vs. placebo (M > P), and placebo vs. naltrexone (P > N). The plotted brackets reflect these model-based contrasts, with test statistics (t-values) and corresponding significance levels derived from the mixed-effects model. This approach allows visualization of raw descriptive patterns alongside inferential comparisons that account for within-subject dependencies and the full experimental design.

Figure 15. DHARMa diagnostics of model 1

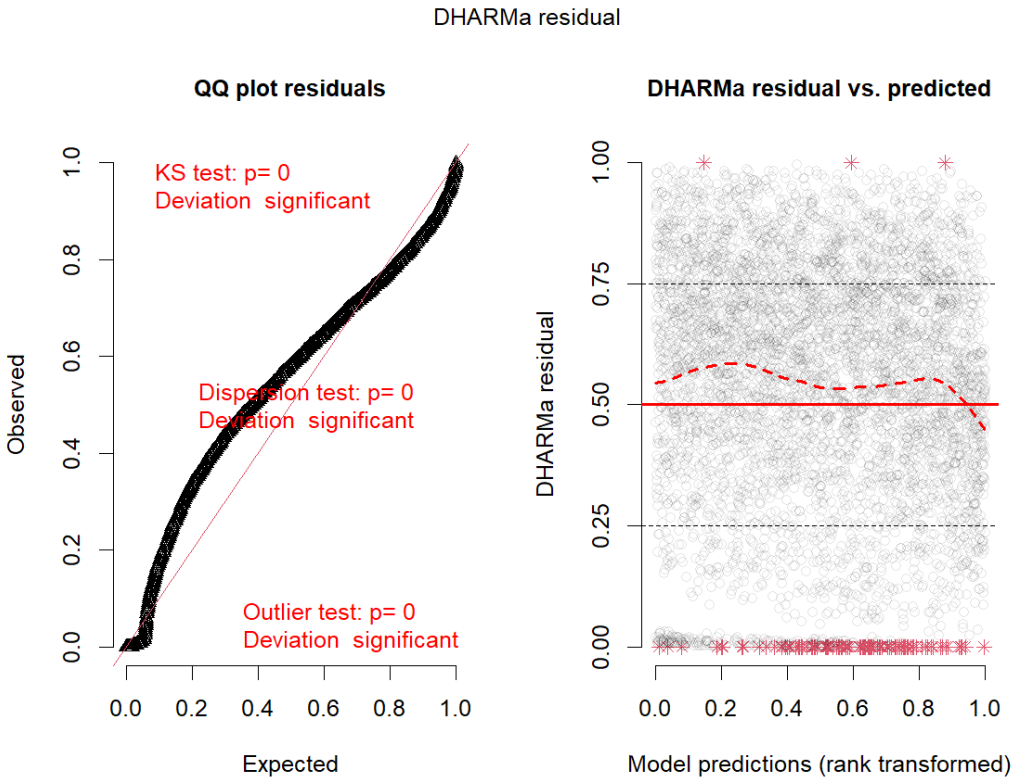


Figure 16. Pearson resiudals vs fitted values plot for model 1

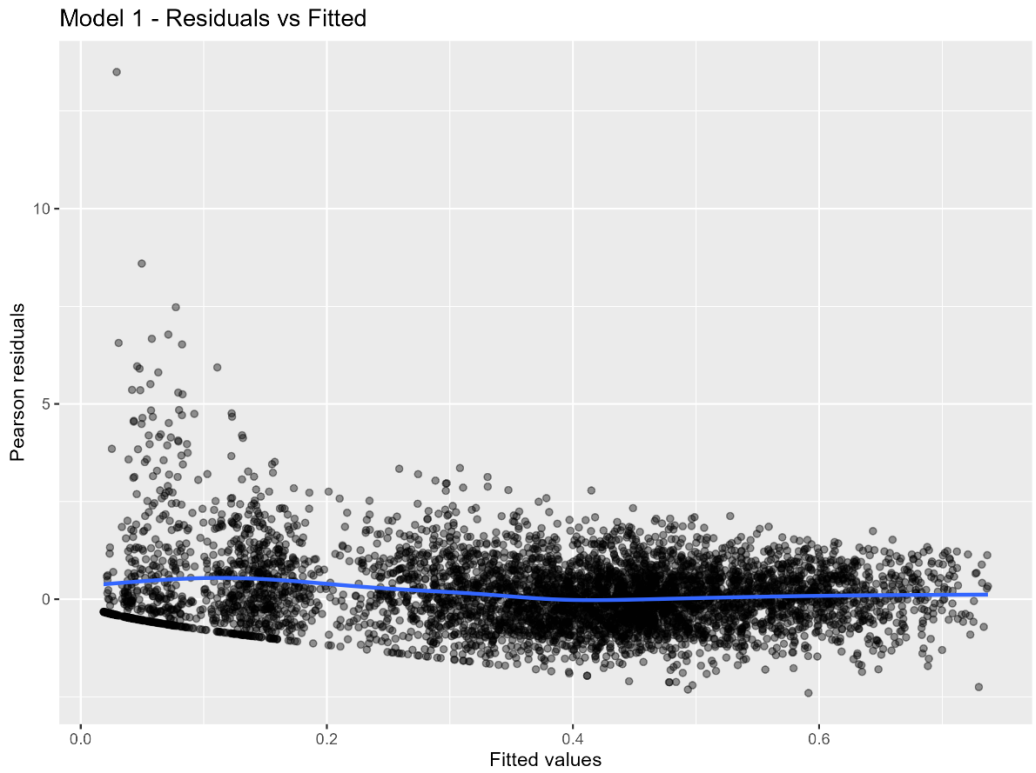
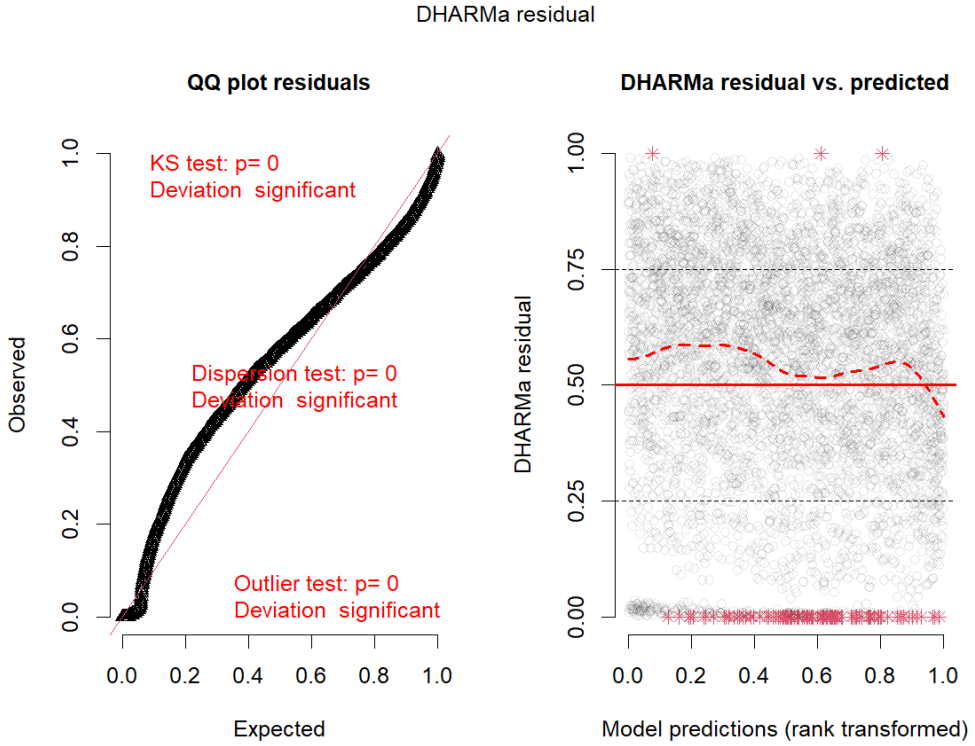


Figure 17: DHARMa diagnostics for model 4



Simulation-based residual diagnostics for the main and robustness models. Visual inspection of DHARMa residual plots indicates deviations from uniformity, mild underdispersion, and an increased proportion of extreme residuals. These patterns were consistent across model specifications. Residuals versus fitted plots further suggest minor systematic structure not captured by the models. Diagnostic plots for Model 1 (Figure 15) show clear deviations from the expected uniform distribution, as indicated by the S-shaped pattern in the QQ plot, alongside evidence of underdispersion and an increased proportion of boundary residuals (0/1). The residuals-versus-predicted panel further indicates mild systematic structure, with a non-flat smooth trend. Complementing this, the Pearson residuals versus fitted values plot (Figure 16) reveals slight curvature and uneven variance across fitted values, suggesting remaining unexplained structure in the data. Figure 17 shows that this pattern is consistent also for the higher complexity models, like model 4. Despite these deviations, the patterns are moderate and do not indicate severe model misspecification and the consistency of results across models supports the robustness of the main effects.

Disclosure of use of AI-tools

DeepL und ChatGPT 5.2 were used not for generating text but grammatical rephrasing and error finding for single sentences and paragraphs. ChatGPT 5.2 was also used for suggestions on condensing information, meaning shortening long sentences or paragraphs. Chat-GPT 5.2 was used in the dataanalysis with R. Prompts involved generating real code from pseudocode descriptions and prompting code for bug-finding and fixing, it was never entirely relied on without understanding of the actual code by the author, meaning it was never used to generate code for entire analysis steps without rechecking each line of code or automation of variable recoding to avoid risk of invisible errors.

Abstracts

English Abstract

Social attention is strongly biased toward faces and, in particular, the eye region, yet substantial individual differences exist in how social cues are prioritized. The present study investigated whether μ-opioid system activity contributes to variability in visual attention to eyes and whether these effects interact with autistic traits and genetic variation in the OPRM1 A118G polymorphism. Using a randomized, double-blind, placebo-controlled within-subject design, 49 healthy adult males completed a face-viewing eye-tracking task under morphine, naltrexone, and placebo conditions. Gaze allocation to the eye region, as a fixation proportion compared to other areas of interest (AOIs), was modelled using generalized linear mixed-effects models (GLMMs). Results showed that μ-opioid agonism (morphine) reliably increased fixation on the eye region, whereas effects of μ-opioid antagonism (naltrexone) were less robust and sensitive to model specification. No significant associations were found between autistic traits and gaze behaviour, nor consistent effects of OPRM1 genotype or its interaction with drug condition. Simulation-based analyses further indicated limited power to detect small genetic effects and interactions. Overall, findings suggest that μ-opioid signalling contributes to modulation of social attention, but its effects are context-dependent and not strongly moderated by subclinical autistic traits or single genetic variation. These results support a nuanced, mechanistic account of social gaze regulation involving opioid-mediated reward processes.

German Abstract

Visuelle Aufmerksamkeit in sozialen Situationen richtet sich bevorzugt auf Gesichter und insbesondere auf die Augenregion, wobei erhebliche interindividuelle Unterschiede in der Priorisierung sozialer Signale bestehen. Diese Masterarbeit untersuchte, ob eine pharmakologische Manipulation des μ-Opioid-Systems (MOR) die visuelle Aufmerksamkeit auf die Augenregion beeinflusst und ob diese Effekte durch subklinische autistische Merkmale sowie genetische Variation im OPRM1 A118G-Polymorphismus moderiert werden. In einer randomisierten, doppelblinden, placebokontrollierten Within-Subject-Studie betrachteten 49 gesunde erwachsene Männer Gesichter in einem Eye-Tracking-Paradigma unter Morphin-, Naltrexon- und Placebo-Bedingungen. Das Blickverhalten auf die Augenregion wurde als Fixationsanteil im Verhältnis zu anderen Interessensbereichen (AOIs) operationalisiert und mittels generalisierter linearer Mixed-Effects-Modelle (GLMMs) analysiert. Die Ergebnisse zeigten, dass MOR-Agonismus (Morphin) die Fixationen auf die Augenregion zuverlässig erhöhte, während die Effekte von MOR-Antagonismus (Naltrexon) weniger robust waren und von der Modellstruktur abhingen. Es fanden sich weder signifikante Zusammenhänge zwischen autistischen Merkmalen und dem Blickverhalten noch konsistente Effekte des OPRM1-Genotyps oder dessen Interaktion mit der Wirkstoffbedingung. Simulationsbasierte Power-Analysen deuteten zudem auf eine zu geringe Power zur Detektion kleiner genetischer Effekte und Interaktionen hin. Insgesamt deuten die Ergebnisse darauf hin, dass das μ-Opioid-System die soziale Aufmerksamkeit moduliert, diese Effekte jedoch kontextabhängig sind und nicht systematisch durch subklinische autistische Merkmale oder einzelne genetische Variationen erklärt werden. Die Ergebnisse unterstützen eine differenzierte, mechanistische Perspektive sozialer Blickregulation unter Beteiligung opioiderger Belohnungsprozesse.