Facing emotions

Towards a better understanding of automatic facial expression processing mechanisms in typical and atypical populations

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DOCTORAL SCHOOL
BIOMEDICAL SCIENCES

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TOWARDS A BETTER UNDERSTANDING OF AUTOMATIC FACIAL EXPRESSION PROCESSING MECHANISMS IN TYPICAL AND ATYPICAL POPULATIONS

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Dissertation presented in partial fulfilment of the requirements for the degree of
Doctor in Biomedical Sciences

September 2020

Dankwoord

Hoewel dit dankwoord in het begin van mijn proefschrift is opgenomen, staat het symbool voor het einde van een fantastisch traject. Het is inderdaad zoals ze zeggen: “De tijd vliegt als je plezier hebt”, want de voorbije vierenhalf jaar zijn voorbij gevlogen. De voorbije jaren waren een fantastische ervaring, een periode waarin ik enorm veel heb bijgeleerd, waarin ik nieuwe mensen leerde kennen en interessante contacten heb gelegd, waarin ik mijzelf heb voelen groeien, maar waarin ik ook heel veel plezier heb gemaakt. Ik wil dit dankwoord dan ook graag richten aan de geweldige mensen die mij vergezeld hebben op mijn reis van klinische psychologe tot waar ik nu ben aanbeland.

“Unagi” *– Ross Geller*

Normaal wordt deze term eigenlijk in een andere context gebruikt, maar ik vond het van toepassing op mijn doctoraatstraject. ‘Unagi’ staat voor een toestand van totaal bewustzijn. Ik ben er nog niet en er valt nog veel te leren, maar ik wil enkele mensen bedanken die de weg richting Unagi in de wereld van frequency-tagging EEG, autismespectrumstoornis (ASS) en emotieverwerking mee hebben geplaveid.

Allereerst, Bart, bedankt voor deze fantastische kans. Bedankt voor het vertrouwen dat een klinisch psychologe toch een volwaardige en waardevolle aanwinst zou kunnen zijn voor je nieuw opstartende onderzoekersteam. Je enthousiasme en gedrevenheid hebben een grote rol gespeeld in mijn groei als onderzoeker. Dankjewel voor je steun en de gecreëerde opportuniteiten.

Milena, I have learnt so much from you. Your door was always open to give advice and to answer questions. You provided an environment in which we could think together and reflect on ideas together, full of constructive feedback, strengthening me in my identity as a researcher. You are the post-doc I would like to be for the other PhD students in our lab. Thank you.

Dit project was niet mogelijk geweest zonder onze deelnemers met ASS. Jean, ik wil jou graag bedanken voor je hulp bij de rekrutering van deze deelnemers, voor je raad en de prettige samenwerking.

Bruno, although you were not officially involved in my PhD project, I would like to thank you for your valuable ideas and for sharing your broad scientific knowledge and expertise.

Ilse en Rufin, dank jullie wel om deel uit te maken van mijn thesis adviescomité. Jullie waardevolle feedback en suggesties, elk vanuit jullie eigen expertise, heeft enorm geholpen om dit werk sterker te maken.

Members of the external jury, Professor van den Boomen and Professor Chakrabarti, thank you for your valuable feedback on this work.

Een dikke merci ook voor de deelnemers en hun ouders. Dank jullie wel om drie keer terug te komen voor de toch wel vermoeiende sessies. Jullie hebben ons geholpen om dit project tot een goed einde te brengen.

"Me and the gang at KUL" – *Monica Geller*

In deze sectie wil ik alle fantastische collega's bedanken, zowel van CDP als van andere onderzoeksgroepen. De oorspronkelijke quote verwijst naar een koffiehuis, maar gezien de sloten koffie die onderzoekers (mezelf inbegrepen) per dag klaarblijkelijk drinken, de gezellige babbels – al dan niet werk-gerelateerd –, en de gemoedelijke sfeer tussen de collega's, zou het even goed over KU Leuven kunnen gaan.

Sarah, Jeroen, Lyssa, Steffie, Matthijs, Silke, Edward, Nicky, Jellina, Sylvie, Jaana en Michelle, jullie zijn geweldig. Zowel binnen als buiten de werkuren. Sofie, jou wil ik in het bijzonder extra hard bedanken. Ik heb van jou super veel geleerd. Ik wil je bedanken voor je engelengeduld om mijn duizenden vragen te beantwoorden, te luisteren naar mijn – vaak nogal uitgebreide – verhalen en om je kennis met veel plezier te delen. Bedankt voor de fijne samenwerking en het echte teamwerk.

Verder wil ik ook de onderzoekers van de bredere onderzoeksgroep Psychiatrie bedanken, alsook de LAuRes-leden. Het was een genoegen om binnen deze verschillende contexten met onderzoekers en ervaringsdeskundigen over specifieke onderwerpen na te denken en te discussiëren.

“She’s a transpon…, transponster” – *Rachel Green*

In deze laatste secties richt ik mij tot enkele belangrijke mensen van buiten het werk. De term ‘transponster’ wordt gebruikt om een job te omschrijven waarvan je deels weet wat het inhoudt, maar toch niet helemaal. Voor vele vrienden en familieleden omvat deze term waarschijnlijk mijn job van de voorbije vierenhalf jaar, met als beschrijvende kernwoorden doctoraat, autisme, hersenen, emotieverwerking. Maar hoewel mijn doctoraat tot op een bepaald niveau abstract is gebleven voor velen van jullie, lieve familie en vrienden, waren jullie oprecht geïnteresseerd in wat ik deed en geloofden jullie in mij. Ik wil jullie hiervoor bedanken. Jullie steun, interesse en fierheid, maar ook het begrip wanneer ik niet over mijn werk wou praten op stressvolle momenten, waren belangrijke bronnen van energie.

Mama, papa, Annelies, Karolien, de jongens, oma, opa, moeke, nonkel Rudi, tante Pascale: dank jullie wel.

Karen, van de vrienden wil ik jou in het bijzonder bedanken. Je bent er altijd – altijd al geweest – voor serieuze babbels of om mijn gedachten te verzetten. Van wandelingen en plezier maken met de twee kleine cuties, over het oplossen van moordzaken tot verwennerij met quiche en kaastaart. Dankjewel voor je eeuwige steun en zorgzaamheid.

“He’s her lobster” – *Phoebe Buffay*

Er blijft dan nog één persoon over die ik nog apart wil bedanken. Volgens Phoebe Buffay – een vrouw vol levenswijsheden – kiezen kreeften een partner voor het leven. Hoewel dit door experten wordt tegengesproken, geloof ik toch dat jij, Yannick, mijn kreeft bent in de betekenis van Phoebe. Ik wil je bedanken voor je geloof in mij, je zorgzaamheid, relativeringsvermogen en je kookkunsten de voorbije jaren en om me onvoorwaardelijk te steunen in mijn ambities, ondanks je eigen ambities.

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Frequently used abbreviations

ANOVA	analysis of variance
AOI	area of interest
ASD	autism spectrum disorder
CPD	cycles per degree
CPI	cycles per image
EEG	electroencephalography
ERP	event-related potential
FFA	fusiform face area
FPVS	fast periodic visual stimulation
HSF	high spatial frequency
LDA	linear discriminant analysis
LMM	linear mixed model
LOT	left occipito-temporal region
LSF	low spatial frequency
MO	medial-occipital region
MSF	middle range spatial frequency
OXT	oxytocin
PL	placebo
ROI	region of interest
ROT	right occipito-temporal region
SF	spatial frequency
SNR	signal-to-noise ratio
TD	typically developing

Summary

As social beings, we often linger in a social environment in which we interact with others. However, these social interactions are not automatically successful and they require social sensitivity and social cognition. One of the key components of social cognition is facial emotion processing. Facial emotion processing expands beyond merely attending to and perceiving facial expression information; it also involves assessing the nature and the importance of the emotional cues to accurately interpret the information and to respond appropriately. In the current doctoral project, we applied different implicit and explicit techniques to enhance our understanding of the underlying mechanisms of automatic facial expression processing and to explore whether these mechanisms are universal.

In a more **fundamental study (Chapter 1)**, we investigated the role of specific spatial frequencies in conveying facial fear. More specifically, we examined which spatial frequency information is minimally required to rapidly and automatically detect fearful faces. Although this has been investigated in many previous studies before, a straightforward conclusion on the relative contribution of low versus high spatial frequencies to facial fear is hampered by, for example, the high variability in demarcations of the spatial frequency spectrum and the high variability in task demands. To move the field forward, we investigated automatic and implicit facial fear processing by systematically sweeping through an entire spatial frequency range using fast periodic visual stimulation (FPVS) in combination with frequency-tagging electroencephalography (EEG). Progressively varying the spatial frequency content of the faces allowed us to pinpoint the threshold of optimal spatial frequency information for the rapid detection of fearful faces, without constraints of predefined cut-offs for low or high spatial frequencies. Our results indicate that implicit facial fear processing mainly requires high spatial frequency information, given its additive beneficial value when added to lower spatial frequencies and its ability to allow rapid facial fear detection by itself. However, explicit facial fear detection involved a slightly broader range of spatial frequencies.

In a series of **applied studies (Chapters 2, 3 and 4)**, we investigated the implicit and explicit facial expression processing of school-aged boys with and without autism spectrum disorder (ASD). Individuals with ASD are characterized by difficulties in social communication and interaction, which are thought to be strongly related to difficulties in emotional face processing. The plethora of behavioural studies on facial expression processing in individuals with and without ASD yields mixed and inconsistent results. These highly variable findings may result from the large variability and limited sensitivity of (certain) behavioural measures. Moreover, the interpretation of explicit emotion processing results can be impeded due to mechanisms beyond facial expression processing per se, such as compensatory mechanisms. Therefore, we focussed on a series of implicit measures to gain more insight in the underlying automatic emotion processing mechanisms that might account for difficulties in facial expression processing in ASD. Here, we applied FPVS combined with frequency-tagging EEG to investigate possible neural differences in facial emotion discrimination between boys with and without ASD. In a first study, we assessed the underlying neural nature of facial fear processing, and whether the neural sensitivity for fearful faces is influenced by the orientation of the faces and by attentional focus to the eyes versus mouth. We found that boys with ASD are less sensitive to rapidly and implicitly detect fearful faces, as compared to typically developing boys, which possibly contributes to emotion processing difficulties. Furthermore, both groups equally display the face inversion effect, suggesting the use of a combined holistic and feature-based face processing style, and both groups equally rely mainly on information from the mouth to detect the fearful expressions. In a second study, we consolidated and expanded these findings by including other facial expressions as well (anger, happiness, sadness) to investigate whether this lower neural sensitivity is emotion-specific or if it generalizes to all emotions. Our findings suggest a rather emotion-specific reduced neural sensitivity, as only fearful and angry faces evoked significantly lower brain responses in comparison to controls. Difficulties in emotion processing may also occur when one fails to inspect the most relevant facial cues. In addition, also spontaneous facial mimicry is found to be related to emotion processing. Spontaneous facial mimicry refers to the automatic movements of face muscles as an implicit response to observed facial emotions. This natural tendency often lacks in individuals with ASD, possibly contributing to emotion processing deficits. Therefore, in a third study, we simultaneously recorded eye gaze patterns and spontaneous facial mimicry of boys with and without ASD during an explicit expression recognition task. Our results suggest that boys with and without ASD employ similar eye gaze strategies to recognize facial expressions, albeit slightly less exploratory in the ASD group. Yet, equal behavioural recognition performances indicate that this does not imply less efficient emotional information processing. Pertaining to the facial mimicry, we found similar facial responses to emotional faces in both groups.

Lastly, in a **clinical intervention study (Chapter 5)**, we investigated the modulatory effects of a single dose of oxytocin on the behavioural and neural sensitivity for facial expression processing in healthy adults. Oxytocin is a neuropeptide that functions as a hormone and neurotransmitter, and has been identified as a key player in social cognition. To date, therapeutic interventions for ASD are mainly based on behavioural social skills trainings, since biomedical therapies or pharmacological interventions targeting social dysfunctions are largely unproven. However, in recent years, intranasal administration of oxytocin has been found to induce behavioural improvements in the social domain in individuals with ASD. To explore its effects on the neural level, we designed a double-blind, within-subjects, cross-over, placebo-controlled oxytocin clinical trial in healthy adult men and applied the previously described frequency-tagging EEG paradigm with multiple expressions. Generally, we found no effect of a single dose of oxytocin on the neural or behavioural emotion processing in healthy men. Possibly, due to the extensive maturation of emotion processing skills in healthy adults, a ceiling-effect might have concealed potential effects of oxytocin. Importantly, personal characteristics, such as social awareness, were found to modulate the effect of oxytocin: oxytocin attenuated the sensitivity to negative expressions, but only in individuals who reported more social difficulties.

Altogether, using a series of implicit measures, this doctoral project contributes to a better understanding of the underlying automatic mechanisms of facial expression processing, both in typical and atypical populations. This broader understanding can further guide therapeutic interventions for ASD, as it could clarify why specific interventions might or might not work. In addition, given the prosocial effect of a single dose of oxytocin found in individuals with more severe social difficulties, this dissertation further paves the way towards a potential pharmacological intervention.

General Introduction

Preamble

Social cognition encompasses different processes that allow interpretation of social information, such as facial expressions, in order to behave appropriately in social situations. At the base of social cognition lies the attention to and perception of relevant, sometimes very subtle, cues. The importance and nature of these cues are determined by rapid, automatic emotion processes, before interpretation of those cues occurs. Based on these interpretations, one can reason about others' intentions, emotions and thoughts, ultimately resulting in a behavioural response.

In terms of emotion processing, which is one of the key components of social cognition, this means that emotional facial cues have to be extracted and processed accurately, to reach a proper interpretation. Hence, accurate emotional face processing precedes theory of mind (i.e. inferring one's mental state based on the processed emotional information) and, eventually, guides behaviour (i.e. to act appropriately). This suggests that social difficulties may be associated with deficits in facial emotion processing.

The aim of this general introduction is to provide an overview of the processing mechanisms underlying and influencing facial emotion processing. **First**, the facial emotion processing in a typical and an atypical population will be outlined from three different perspectives. In the **second** section, we will depict the automatic strategies to extract the valuable emotional information from faces. In a **third** section, we briefly touch upon the mediating effect of oxytocin on emotional face processing. **Lastly**, the mainly applied technique and the general aim of this doctoral project will be described, and we will provide a comprehensive overview of the studies presented in the following chapters of this dissertation.

1. Typical and atypical facial emotion processing

1.1 From a behavioural perspective

1.1.1 Development in a typical population

The importance of the correct interpretation of emotional signals for successful social interactions is unchallenged. Typically, from very early infancy, humans learn to understand the cues they perceive in a face to respond appropriately to their surroundings. Typically developing infants are already capable of discriminating between angry and happy faces (Barrera & Maurer, 1981), and even between happy, angry, sad and fearful faces in a familiar context (Haggerty, 1998) at a few months of age. However, initially, infants, toddlers and very young pre-schoolers tend to use broad valence- and arousal-based categories to understand facial expressions (for a review, see (Widen & Russell, 2008)) and only gradually learn to categorize them as specific discrete emotions throughout development (Widen, 2013).

Indeed, facial emotion processing **typically develops and improves with age** (De Sonneville et al., 2002; Herba et al., 2006; Luyster et al., 2017; Mancini et al., 2013), but the developmental trajectories are emotion-specific (Herba, 2006; Herba & Phillips, 2004). From the six basic expressions (i.e. anger, fear, happiness, sadness, disgust and surprise, (Ekman, 1992)) happiness is recognized the earliest, fastest and most accurate (De Sonneville, 2002; Herba, 2004; Mancini, 2013), needing only minimal signals (Luyster, 2017; Rodger et al., 2015). The recognition of happiness reaches adult levels at five to six years of age and remains stable, while the recognition of other prototypical expressions reaches maturity at approximately ten years of age (Durand et al., 2007; Lawrence et al., 2015; Mancini, 2013; Rodger, 2015). However, the lack of improvement in proficiency for recognizing facial expressions after the age of ten might be due to performance ceiling effects (Rump et al., 2009). The developmental trajectories of sadness and surprise recognition evolve slower and more gradually (Chronaki et al., 2015; Lawrence, 2015; Rodger, 2015), whereas explicit recognition of anger shows a steeper improvement (Ewing et al., 2017; Rodger, 2015), with a clear increase in sensitivity from adolescence into adulthood (Lawrence, 2015; Thomas et al., 2007). As for fear recognition, most studies show a linear increase from childhood into adulthood (Durand, 2007; Ewing, 2017;

Lawrence, 2015; Thomas, 2007). Rodger and colleagues (Rodger, 2015), however, found a stable fear recognition from five years on. Difficulties with more complex and less intense expressions may persist into adolescence before reaching full development in adulthood (Bayet & Nelson, 2019; De Sonneville, 2002; Herba, 2006; Lawrence, 2015; Thomas, 2007).

1.1.2 Development in individuals with autism spectrum disorder

Autism spectrum disorder (ASD) is a neurodevelopmental disorder with impairments in social communication and interaction as one of its core characteristics, including deficits in socio-emotional reciprocity and deficient non-verbal communicative behaviour, among others (American Psychiatric Association, 2014). Given the importance of facial expressions as nonverbal sources for emotional communication, the social symptoms of ASD may be strongly associated with deficits in emotional face processing (Bölte & Prouska, 2003; Farran et al., 2011; Schultz, 2005).

The age-related improvement in facial emotion processing that is seen in typically developing (TD) individuals seems to be absent (Gepner, 2001; Rump, 2009), or at least less pronounced (Trevisan & Birmingham, 2016) in individuals with ASD. Based on the increased magnitude of facial emotion processing deficits in ASD over time, a recent meta-analysis concluded on a **rather flattened development** as compared to the steadily improving development in TDs (Lozier et al., 2014). More specifically, the gap in emotion processing abilities in individuals with and without ASD widened with age: differences in facial emotion processing were least pronounced in children and became more distinct in adults (Lozier, 2014). Indeed, child studies often do not report differences between ASD and TD groups (Lacroix et al., 2014; Law Smith et al., 2010; Tracy et al., 2011), possibly due to the still ongoing development of emotion recognition during childhood, with low performances in the control group concealing possible group differences.

1.1.3 Differences in behavioural emotion processing in individuals with and without ASD

An abundance of behavioural studies has investigated the emotion processing abilities of individuals with and without ASD, yielding, however, **mixed and inconsistent results** (Harms et al., 2010; Jemel et al., 2006; Lozier, 2014; Nuske et al., 2013; Uljarevic & Hamilton, 2013). Most studies suggest a general emotion processing deficit in ASD as compared to TD controls (Evers, 2015; Fridenson-Hayo et al., 2016; Luckhardt et al., 2017; Xavier et al., 2015), although some researchers only find impairments for specific – mostly negative – emotions (Griffiths et al., 2017; Law Smith, 2010; Whitaker et al., 2017; Wingenbach et al., 2017). Fear has been shown a difficult to recognize expression for individuals with ASD, especially for adults (Lozier, 2014; Rump, 2009). In addition, some studies also reported differences in recognition abilities for positive emotions, such as surprise (Law Smith, 2010) and happiness (Griffiths, 2017). Generally, though, individuals with and without ASD perform equally well for happy facial expressions (Law Smith, 2010; Whitaker, 2017; Wingenbach, 2017). As opposed to the findings described before, other studies have reported intact facial expression recognition (Lacroix, 2014; Leung et al., 2013; Tracy, 2011). Intact recognition abilities may indicate the use of verbally mediated or cognitive compensatory mechanisms in ASD to recognize facial expressions, whereas this process is more automatic in TDs (Harms, 2010). Hence, the interpretation of explicit emotion processing results can be impeded due to mechanisms beyond facial expression processing per se.

A considerable degree of the conflicting findings can be attributed to task demands, as higher task demands increase the likelihood of observing deficits in individuals with ASD (Harms, 2010). For example, facial emotion processing is worse in individuals with ASD as compared to TDs when stimuli are only shortly presented (Rump, 2009) or presented at lower intensities (Griffiths, 2017; Wingenbach, 2017). Furthermore, most studies find facial emotion processing problems in ASD when complex or more subtle emotions are included (Law Smith, 2010), versus explicit basic emotion recognition tasks (Deruelle et al., 2004; Leung, 2013; Tracy, 2011). Considering the potential confounding influences of task demands on explicit emotion recognition, the highly variable behavioural results may reflect the variability and limited sensitivity of (certain) behavioural measures (Harms, 2010).

1.2 From a neural perspective

Facial expression processing entails more than merely the behavioural output of explicit recognition. Extracting meaning from facial expressions involves a network of cortical regions in the ventral occipito-temporal cortex and superior temporal cortex that all extract different types of information for accurate interpretation (Haxby & Gobbini, 2011). The core system of this face processing network comprises the occipital and fusiform gyri (also known as the occipital and fusiform face area (OFA and FFA), respectively (Kanwisher et al., 1997)), which are involved in identifying faces based on invariant features, as well as the posterior superior temporal sulcus (STS) to process the dynamic face parts (Gobbini & Haxby, 2007; Haxby, 2011). This core face processing system – especially the STS – is activated when processing expressive faces, along with areas of the extended system associated with either the valence (e.g. amygdala) or the production (e.g. frontal operculum) of facial expressions (Haxby, 2011; Zinchenko et al., 2018) (Fig.1).

More specifically, perceiving particularly dynamic facial expressions evokes activity in the frontal operculum, which is part of the putative mirror neuron system (Haxby, 2011). This area is assumed to derive meaning from the visual facial input by engaging the motor representations for facial expression production (Carr et al., 2013). In addition, brain areas associated with emotion (e.g. amygdala) are also activated (Fig.1), indicating that the emotion itself is evoked to understand the emotional meaning of the perceived expression, yet, without leading to the explicit experience of that emotion (Haxby, 2011).

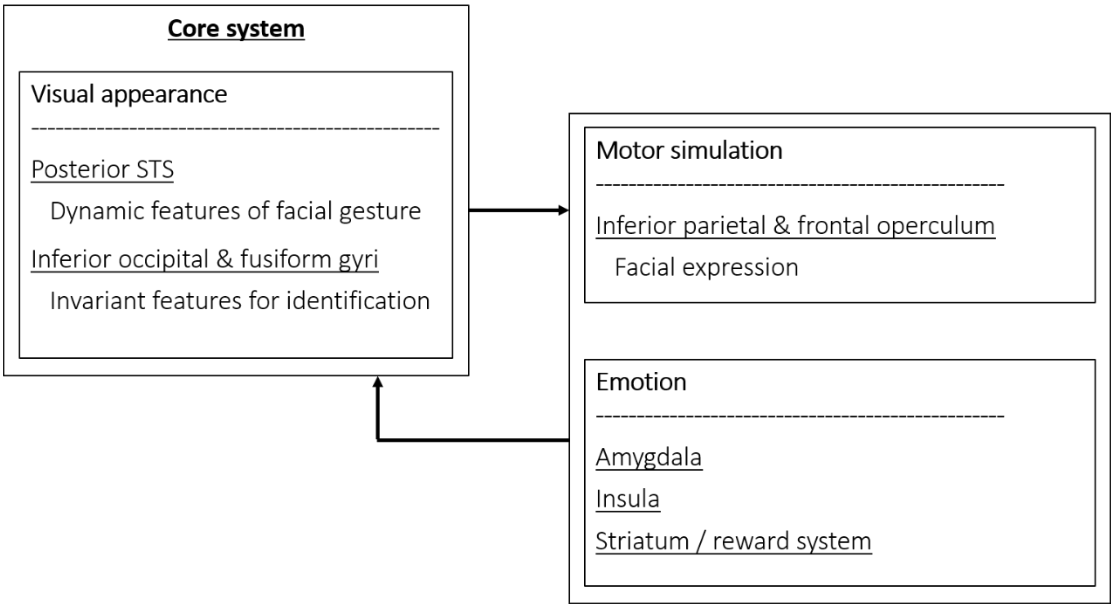

Figure 1. Neural systems of the face processing network specifically involved in facial expression processing. STS = superior temporal sulcus. Adapted from The Oxford Handbook of Face Perception (p.105), by J. V. Haxby and M. I. Gobbini, 2011, Oxford University Press.

Mostly, one of two neuroimaging methods – functional magnetic resonance imaging (fMRI) or electroencephalography (EEG) – is applied to disentangle the neural correlates of facial expression processing.

1.2.1 Development in a typical population

Although the key brain regions involved in emotional face processing already develop early after birth, their neural **specialization for expressive faces increases gradually over time**. Indeed, event-related potential (ERP) studies show that the regions involved in face processing are already activated at the age of three months during face perception (for a review, see (De Haan et al., 2003)). However, these neural populations react to a broader range of stimuli as compared to adults, suggesting the tuning of these regions to human faces over time (De Haan, 2003; Leppänen & Nelson, 2009). In addition, connections between the visual and the orbitofrontal cortex – already established at nine months of age when viewing happy versus neutral faces (Minagawa-Kawai et al., 2009) – indicate the effective processing of these positive-affective cues. Moreover, infants as young as seven months present a clear fear bias, reflected in larger ERP responses to fearful as compared to neutral faces and activations of the brain areas involved in the orientation of attentional resources (for a review, see (Bayet, 2019)). These results demonstrate that the tendency to attend more to socially salient stimuli is already present at a very young age.

Whereas the neural responses to different facial expressions during the first few months of life seem to rely mainly on facial features, rather than the emotional content, a recent review concluded on a first maturation process around six to seven months of age with the emergence of the discrete emotion categories happiness, anger and fear (Bayet, 2019). The evolution of the neural specialization continues throughout childhood (Haist & Anzures, 2017), where the lateralization patterns – indicative of the involvement of higher-level brain areas – are strengthened (for a review, see (Watling et al., 2012)) and goes through a second period of profound maturation in terms of activity and connectivity during adolescence (Blakemore, 2008; Nelson et al., 2005).

Maturation of the facial emotion processing abilities has been attributed to two different plasticity mechanisms related to the storage of perceived information: experience-expectant and experience-dependent mechanisms. Experience-expectant plasticity entails the generalized development of the brain based on common experiences that all humans are exposed to during constrained, critical time periods (Greenough et al., 2008). The bias of infants to attend to biologically salient cues, such as fearful faces, without being able to derive meaning from them or to understand why they are prompted to look at these faces, is a clear example (Leppänen, 2011). The perceptual representations of the facial expressions formed via the experience-expectant mechanisms are further shaped by the frequency and the intensities of the facial expressions one experiences in his or her own environment (i.e. experience-dependent) (Greenough, 2008). Studies with maltreated children provide clear evidence to support this: their facial expression recognition abilities are generally similar to those of non-maltreated children, yet, they demonstrate a notably augmented sensitivity and a broader perceptual category for cues signalling anger (Pollak et al., 2000; Pollak & Kistler, 2002). Given their similar emotion recognition performances in general, this is suggestive of a tuning shift to the representations of these facial expressions, rather than an alteration of these representations (Leppänen, 2009).

1.2.2 Development in individuals with autism spectrum disorder

Current literature concerning the developmental trajectory of neural facial expression processing in ASD is scarce. Two neural characteristics that seem consistent across the lifespan are reduced amygdala activity (Ashwin et al., 2007; Corbett et al., 2009; South et al., 2008) and hypo-activation of the FFA (for a review, see (Schultz, 2005)). Furthermore, decreased latencies and amplitudes of the P1 and the N170 ERP components while processing emotional faces are associated with increasing age in ASD; an effect also found in typical populations (Batty et al., 2011; O'Connor et al., 2005). However, opposite results have also been reported, with higher amplitudes for the P1 component for older participants (Tye et al., 2014).

In addition, specificities in functional connectivity between the amygdala and the frontal cortex seem to persist from adolescence into adulthood (Bachevalier & Loveland, 2006; Odriozola et al., 2019). As these brain regions are employed when perceiving and assessing socio-emotional information, the atypical connectivity might be associated with more severe social difficulties and less social orienting (Chevallier et al., 2012). Considering the importance of experiences in tuning the brain towards social signals, deprivation of social interactions might hamper further maturation of the emotion processing abilities. According to the **social motivation theory** (Chevallier, 2012), individuals with ASD show a reduced tendency to orient to social stimuli and to maintain social interactions. Furthermore, engaging in social interactions seems to be less rewarding for individuals with ASD, as compared to TDs (Clements et al., 2018). As many individuals with ASD tend to participate in fewer social interactions in comparison to TD individuals from a young age on (Lord & Magill-Evans, 1995), they might not acquire the emotional face processing experiences necessary for typical maturity of these abilities.

1.2.3 Differences in neural emotion processing in individuals with and without ASD

Many researchers have turned to fMRI to probe the brain activity and/or connectivity during emotional face processing in individuals with and without ASD, with the focus on two regions that are heavily involved in emotion perception (Phillips et al., 2003): the FFA and the amygdala, as well as its connection to the prefrontal cortex. Regarding the FFA, literature yields mixed results involving either hypo-activation in individuals with ASD as compared to TDs during different emotional face processing tasks (Nomi & Uddin, 2015; Schultz, 2005), or similar activation patterns (Bird et al., 2006; Hadjikhani et al., 2004), which was recently supported by a meta-analysis (Aoki et al., 2015). Pertaining to the amygdala and its interconnectedness with the prefrontal cortex, the Amygdala Theory of Autism posits that atypicalities in the amygdala are the root of the social deficits characteristic for ASD (Baron-Cohen et al., 2000). Hypo-activation of this region has, indeed, frequently been found (for a meta-analysis, see Aoki, 2015), especially when processing fearful faces (Ashwin, 2007; Kim et al., 2015). In addition, substantial evidence points towards a dysfunctional connectivity between the amygdala and the prefrontal cortex (for a review, see Bachevalier, 2006), possibly resulting in the socio-emotional difficulties in ASD.

In addition to fMRI, EEG is a suitable method for ASD research, given its non-invasive nature and the non-requirement of verbal or motor responses (Webb et al., 2015). ERPs have been widely used to investigate perceptual mechanisms supporting face and emotion processing abilities in individuals with and without ASD (Jeste & Nelson, 2009; Key & Corbett, 2014;

Lerner et al., 2013; Monteiro et al., 2017). However, up until now, ERP studies have also **generally failed to draw consistent conclusions** on facially expressed emotion processing in ASD (Black et al., 2017; Harms, 2010). Some studies report similar ERP patterns in children and adolescents with ASD compared to TD controls (Apicella et al., 2013; O'Connor, 2005; Wong et al., 2008), whereas others report differences. Differences in latency and/or amplitudes have frequently been found in early ERP components, such as P100 (Batty, 2011; Luckhardt, 2017), N170 (Batty, 2011; Luyster, 2017; Tye, 2014) and N300 (Dawson et al., 2004), suggesting reduced or delayed emotional face processing. However, anomalies have also been reported in later ERP components (e.g. N400 (Tye, 2014) or negative slow wave (Dawson, 2004)), which are believed to be more related to emotion categorization than to affective processing (Calvo & Nummenmaa, 2015; for a review, see Monteiro, 2017). Differences in ERP components, particularly in the N170, between both groups have often been reported for fearful faces (Dawson, 2004; De Jong et al., 2008; Tye, 2014).

This N170 component is of particular interest for (expressive) face processing (Hinojosa et al., 2015). Recently, Kang and colleagues (2018) proposed the N170 as a possible biomarker of the underlying neural face processing deficits in individuals with ASD. However, the differences found between ASD and TD could merely reflect a slower general processing of social stimuli (Hileman et al., 2011; Lerner, 2013; Luyster, 2017; Vettori et al., 2018) or they could be caused by carryover effects from changes in the amplitude and/or latency of the immediately preceding P100 component (Hileman, 2011). In addition, atypicalities in the N170 response to emotional faces (i.e. delayed and/or reduced response) may not be autism-specific: similar atypical N170 responses have been observed in other psychiatric and neurological disorders and may rather be an indication of emotional face processing dysfunction as a symptom of these diagnoses, than disorder-specific deficits (Feuerriegel et al., 2015).

1.3 From an embodied perspective

A framework of embodied simulation proposes that individuals use their body to understand the emotions facially expressed by others (Wood et al., 2016). More specifically, spontaneously mimicking a perceived expression might support its perceptual recognition by the subjective experience of the emotion, caused by feedback from the facial muscles that are activated, to the neural system (Hess & Fischer, 2014; McIntosh, 1996). Indeed, numerous studies have suggested that, typically, spontaneous facial mimicry is associated with emotion recognition (Borgomaneri et al., 2020; Lakin, 2013; Ponari et al., 2012).

1.3.1 Development in a typical population

Spontaneous facial mimicry can be defined as the unintended unconscious mirroring of others' emotional facial expressions, which leads to congruent facial muscle activity within the first few seconds after seeing one's expression (Mathersul et al., 2013; Moody et al., 2018; Oberman et al., 2009).

To date, still relatively little is known about the developmental process of facial mimicry. Although several studies have investigated the behavioural mimicry of infants, including non-emotional facial movements, only few studies have investigated emotional facial mimicry. These studies have shown that the spontaneous mimicry of facial expressions is an early emerging phenomenon that **occurs from 5 months of age** and continues to develop. Whereas 4-month old infants did not display any facial activation to the presented facial expressions (Kaiser et al., 2017), 5-month olds demonstrated facial mimicry for sad and happy dynamic facial expressions (Isomura et al., 2014). Yet, only during the multimodal audiovisual presentation; the unimodal visual stimuli did not elicit facial responses. In addition, facial mimicry responses were reported in 7-month old infants for dynamic happy and fearful faces (Kaiser, 2017). Toddlers, aged three, presented facial mimicry for happy and angry facial expressions (Geangu et al., 2016). In both these latter age groups, unimodal visual stimulus presentation evoked facial mimicry.

Studies investigating the development of facial mimicry in individuals with ASD seem to be non-existent.

1.3.2 Differences in facial mimicry in individuals with and without ASD

TD individuals have the natural tendency to mirror the facial expressions of their interaction partner (Duffy & Chartrand, 2015; Lakin, 2013; Sonnby-Borgström, 2016), as it facilitates affiliation (Kavanagh & Winkielman, 2016; Lakin & Chartrand, 2003), fosters affective and cognitive empathy towards each other (Drimalla et al., 2019) and boosts prosocial behavior (Stel et al., 2010; Van Baaren et al., 2004). However, facial mimicry can also be evoked in standardized laboratory situations, using pictures of emotional faces (Borgomaneri, 2020; Lehane, 2015), without an explicit social context present.

This default tendency to automatically mimic the facial expressions of the interaction partner may lack in individuals with ASD (Moody & McIntosh, 2006; Vivanti & Hamilton, 2014). Indeed, although some studies using facial electromyography (EMG) or the Facial Action Coding System (FACS; (Ekman & Friesen, 1978)) reported intact (Deschamps et al., 2013; Schulte-Rüther et al., 2017) or even enhanced facial mimicry (Magnée et al., 2007), majority of the studies found **reduced or delayed facial mimicry** to different facial expressions in adults (McIntosh et al., 2006; Yoshimura et al., 2015) and children (Beall et al., 2008; Oberman, 2009; Stel et al., 2008) with ASD, as compared to TDs. Importantly, considering the simultaneously reported intact voluntary facial mimicry (McIntosh, 2006; Oberman, 2009; Stel, 2008), this deficit was not due to impairments in perception or praxis.

If facial feedback indeed affects emotion recognition, and individuals with ASD are less likely to mimic facial expressions, deficits in facial mimicry might play a critical role in the social functioning of individuals with ASD.

2. Facial emotion processing: extracting critical facial information

As emotional faces convey a wealth of information, one needs to extract the most important information in order to accurately and efficiently process the expression. Particularly of interest here are the spatial frequencies the face and its features are comprised of, as well as these facial features themselves.

2.1 The importance of particular spatial frequencies

Spatial frequencies (SFs) are the basic components of visual information, characterized by their spatial distribution of luminance variations (De Valois & De Valois, 1980). In general, low spatial frequencies (LSFs) are believed to convey the coarse, general contours of the face, whereas high spatial frequencies (HSFs) convey the more detailed, specific facial features (Fig.2).

This information needs to be extracted fast and efficiently during social interactions in order to be able to **act appropriately in every situation** (Ruiz-Soler & Beltran, 2006). Generally, it is assumed that this extraction occurs in a fixed coarse-to-fine sequence, with the coarse and global LSFs being processed first, subsequently followed by the extraction of the fine and more local HSF information (Cheung et al., 2008; De Cesarei & Codispoti, 2013). In this sequence, the relatively quickly processed LSF information allows a stable but tentative expression recognition and requires the additional HSFs for accurate and robust emotion categorization (Morrison & Schyns, 2001; Oliva & Schyns, 1997). However, other researchers have argued in favour of a more flexible use of spatial frequencies rather than a fixed one, where the critical, diagnostic SF information varies based on task demands and stimulus properties (Morrison, 2001; Ruiz-Soler, 2006). Hence, the integration of facial information can also follow a fine-to-coarse sequence.

Figure 2. Faces convey a spectrum of low and high spatial frequencies. ***Upper right panel****: a face comprising only low spatial frequencies, which are believed to convey the coarse, general contours of the face.* ***Lower right panel****: a face comprising only high spatial frequencies, conveying the more detailed, specific facial features. This stimulus was selected from the Karolinska Directed Emotional Faces database (KDEF; Lundqvist et al. 1998); stimulus shown here is AM05.*

To gain more insight in how the visual system processes faces, several studies have attempted to pinpoint the range of SFs that play the most crucial role in (different aspects of) face processing. Various cut-offs to define the LSFs and HSFs have been explored in the literature, but, very roughly, the demarcations can be considered as follows (in cycles per image, cpi; (Schyns & Oliva, 1999; Vuilleumier et al., 2003; S. Wang et al., 2015)):

- LSFs: SFs < 8 cpi
- Middle range SFs (MSFs): 8 cpi < SFs < 24 cpi
- HSFs: SFs > 24 cpi

For face processing in general, the importance of LSF information has been emphasized, implying that HSFs are redundant (Canário et al., 2016; Goffaux et al., 2003). Yet, other studies found evidence in support of a HSF bias for face processing (Flevaris et al., 2008; Halit et al., 2006). Generally, though, the MSF range has been suggested as the optimal frequency range for face processing (Morrison, 2001; Ruiz-Soler, 2006). These findings already allude to the difficulties of understanding the role of specific SFs for facial emotion processing.

Indeed, regarding the role of SFs in emotional face processing, results on the preferential sensitivity for specific SFs are conflicting (for reviews, see De Cesarei, 2013; Jeantet et al., 2018). For example, whereas sadness has been found to rely mainly on HSFs (Kumar & Srinivasan, 2011), other studies show that sadness is recognized based on LSF information (Schyns, 1999). Studies investigating the role of SF information for the processing of fear have also reported mixed findings, either suggestive of a preference for LSFs in comparison to neutral (Vlamings et al., 2009; Vuilleumier, 2003) and happy faces (Morawetz et al., 2011), or for HSFs as opposed to other facial expressions (Smith & Merlusca, 2014; Stein et al., 2014). For happiness, results are more consistent and indicate a LSF bias (Kumar, 2011; Wang, 2015). Furthermore, in support of the more flexible use of spatial frequencies during emotional face processing, literature has also demonstrated the mediating influence of task demands: detecting and categorizing facial emotions rely primarily on LSFs and HSFs, respectively (Schyns, 1999). In addition to task demands, also other methodological decisions have been found to mediate the preference for specific SFs. In particular, shorter presentation durations seem to favour LSFs, whereas HSFs are predominantly used when stimuli are presented longer (Aguado et al., 2010; Wang, 2015). Moreover, several experimental parameters (e.g. stimulus size, viewing distance, luminance, etc.) affect the visual angle and might, in extension, change the actual SF information that is received by the retina (Wang, 2015).

As the above-described evidence signifies, the large methodological variability across studies contributes to the inconsistencies encountered in the literature (De Cesarei, 2013). Furthermore, comparison across studies is also hampered by the use of different units to express the SF content of the stimuli, as well as by the inconsistent definitions of HSFs and LSFs (Jeantet, 2018). Hence, although SF extraction is substantial to facial emotion processing, the exact nature of the importance remains ambiguous.

2.2 The importance of particular facial features

In addition to the SFs of which the face and its features are comprised, emotional information can also be extracted from these facial features directly.

Indeed, different face regions display information necessary to decode specific emotions. Hence, when processing emotional faces, individuals tend to vary their scanning patterns depending on the emotional content of the face (Beaudry et al., 2014). In particular, they fixate more on the mouth versus the eyes for positive versus negative emotions, respectively (Eisenbarth & Alpers, 2011; Wegrzyn et al., 2017). These augmented fixations on either the lower or the upper part of the face seem to be associated with the most informative facial cues for specific facial expressions. For example, happiness is, indeed, more easily recognized from the mouth (Beaudry, 2014; Bombari et al., 2013; Eisenbarth, 2011). Likewise, processing of sadness and anger seems to rely mostly on information from the eye region (Eisenbarth, 2011; Guarnera et al., 2017). For fear, literature reveals mixed findings, suggesting the significance of the eyes (Bombari, 2013), equal significance of both the eyes and the mouth (Eisenbarth, 2011), or demonstrating the necessity of the combination of the eyes and mouth (Beaudry, 2014).

Individuals with ASD also seem to display **varied scanning of faces as a function of facial expression** (de Wit et al., 2008), albeit, less pronounced than in TDs (Åsberg Johnels et al., 2017). Furthermore, comparison of their eye gaze patterns to patterns demonstrated by TDs yields mixed results (Black, 2017; Papagiannopoulou et al., 2014). Similar eye gaze patterns during emotional face processing have been reported, with equal gaze to the eyes of positive and negative expressions in both groups (Falck-ytter et al., 2010; Leung, 2013), or, on the contrary, better expression recognition in both groups when relying on information from the mouth (McMahon et al., 2016), as well as a comparable number of fixations on specific facial cues (Leung, 2013; Van der Geest et al., 2002). Yet, contradicting results, indicating divergent face scanning, have also been found: both implicit and explicit tasks have revealed a preferential looking towards the mouth instead of the eyes in children with ASD, as compared to TD children (Bal et al., 2010; Nuske et al., 2014), or a tendency to look more outside the core facial features in both children (Nuske, 2014) and adults (Pelphrey et al., 2002) with ASD. In addition, researchers also observed differences in fixation duration, with shorter fixations in individuals with ASD when looking at fearful faces (Nuske, 2014) or rather longer fixations irrespective of facial expression (Leung, 2013).

Yet, a similar way of looking at faces to read emotions does not automatically imply a similar level of emotion recognition performance (Sawyer et al., 2012).

2.3 The importance of adopting the most optimal perceptual strategy

Difficulties in emotion processing may thus occur when one fails to inspect the most relevant facial cues (Ellison & Massaro, 1997). This is closely related to the perceptual strategy employed when extracting critical facial information.

Typically, faces are processed in a global, holistic manner: they are recognized by integrating facial features into a holistic representation, rather than by relying on those facial features separately (Tanaka & Farah, 1993). The face-inversion effect is a commonly used method to investigate one’s processing style. More specifically, if a **holistic processing style** is applied, inversion will impair the recognition of the face as opposed to when it is presented upright (Rossion, 2013). TD individuals apply this approach when processing (expressive) faces. Indeed, when faces are inverted, the holistic processing is disrupted in TDs, prompting them to rely more on individual facial features (Durand, 2007).

In contrast, a more **local, feature-based approach** implies that the recognition of (emotional) faces depends on the individual face parts (Ellison, 1997). Although individuals typically apply a holistic perceptual strategy, studies investigating facial emotion processing have also lend support to the feature-based processing style. For example, happy and angry faces could reliably be categorized based on separate facial features (e.g. eye brows), without the necessity of a whole face (Ellison, 1997).

These findings clearly hint at the importance of the applied perceptual processing strategy. More specifically, whereas some facial expressions require the whole face to process (i.e. holistic), others can be recognized based on a simple facial feature (i.e. feature-based) (Beaudry, 2014; Guarnera, 2017). Hence, failing to adjust the perceptual strategy to the requirements of particular emotions might result in expression processing difficulties when critical emotional information is missed.

Considering that the absence of an inversion-effect has often been reported in studies with individuals with ASD (Behrmann et al., 2006), this suggests the use of a feature-based approach. However, nuances are in place, as better emotion recognition in upright versus inverted faces – common for TDs – has also been observed in individuals with ASD (McMahon, 2016). This implies that individuals with ASD are capable of holistic face processing. Indeed, a meta-analysis provided evidence to support this claim: generally, the local, feature-based processing style is more automatic and spontaneous for individuals with ASD, but they are capable of global processing. They just take longer to perceive the global picture than TDs (Van der Hallen et al., 2014). However, given that this meta-analysis was based solely on studies employing non-face paradigms, the question remains whether these shifts in processing style would also apply during (emotional) face processing.

3. The effect of intranasal oxytocin on facial emotion processing

Endogenous oxytocin (OXT) is a neuropeptide that is produced in the hypothalamus and functions as a hormone and a neuromodulator of prosocial behaviour and socio-cognitive processes (MacDonald & MacDonald, 2010; McClung et al., 2018; Viero et al., 2010; Wigton et al., 2015). Central OXT levels can, however, be manipulated by intranasally administered exogenous OXT (Quintana et al., 2018). Generally, it has been thought to invariantly improve prosocial behaviour and social cognition, but reviews have highlighted its variable nature, determined by person-dependent factors and the social context (Bartz et al., 2011; Evans et al., 2014). For instance, effects of exogenous OXT have mainly been observed in those individuals who initially (i.e. before OXT treatment) scored low in terms of social-cognitive competence (Bartz, Zaki, Bolger, et al., 2010), and high on anxious attachment (Bartz, Zaki, Ochsner, et al., 2010; Bartz et al., 2011).

Mechanistic models suggest that OXT may exert its complex ‘prosocial’ effects by regulating the saliency of social cues and/or by modulating (social) stress and anxiety (Bartz, 2011; Churchland & Winkielman, 2012; Shamay-Tsoory & Abu-Akel, 2016), which can be of particular interest for facial emotion recognition. Indeed, many behavioural studies have sought to elucidate how OXT affects facial expression processing. Despite the overall idea of OXT enhancing emotion recognition, closer inspection of the findings reveals rather attenuated and inconsistent results (for reviews and a meta-analysis, see Bartz, 2011; Evans, 2014; Leppanen et al., 2017; Shahrestani et al., 2013; Van IJzendoorn & Bakermans-Kranenburg, 2012). Whereas some studies found an overall **improvement of facial expression recognition**, irrespective of the valence of the expressions (Guastella et al., 2010; Lischke et al., 2012), others have reported an OXT effect for positive (Di Simplicio et al., 2009; Marsh et al., 2010; Schulze et al., 2011) or negative (Fischer-Shofty et al., 2010) emotions only. In a similar vein, OXT has been found to modulate the approach-avoidance tendency, by facilitating sensitivity for positive emotional stimuli (Kemp & Guastella, 2011; Kemp et al., 2012; Radke et al., 2013) and attenuating sensitivity for negative emotional stimuli (Ellenbogen, 2018). Moreover, some studies showed that the OXT induced improvement was dependent on task difficulty (Domes, Heinrichs, Michel, et al., 2007; Guastella, 2010).

At a neural level – as investigated via fMRI – a single dose of OXT commonly shows attenuated amygdala activity, mostly in response to negative social stimuli (for meta-analyses, see Grace et al., 2018; Wang et al., 2017), which is considered to reflect a reduction in social anxiety. Yet, similar to the behavioural data, results vary and point into different directions. For example, while attenuated amygdala activity has been reported during implicit and explicit processing of both positive (Domes, Heinrichs, Gläscher, et al., 2007) and negative (Domes, 2007; Gamer et al., 2010; Kirsch et al., 2005) emotions, enhanced amygdala activity for happy faces has also been reported (Gamer, 2010). Furthermore, in women, a single dose of OXT enhanced activity in different brain regions in relation to specific facial emotions (Domes et al., 2010): increased activation for angry faces was reported in the inferior frontal gyrus and ventro-lateral prefrontal regions, for happy faces in the inferior frontal gyrus and the fusiform gyrus, and for fearful faces in the medial and superior temporal cortex and the bilateral fusiform gyrus. In addition, OXT also augments functional connectivity between the amygdala and the reward system (Wang, 2017) or the salience network (Grace, 2018; Wang, 2017). Moreover, a recent meta-analysis proposed increased activity in the superior temporal gyrus resulting from OXT administration as the main factor for improved emotion recognition (Grace, 2018).

ERP studies investigating emotional face processing, on the other hand, reported modulatory effects of OXT on earlier ERP components. For instance, shorter latencies of the N170 component were observed (Tillman et al., 2019), as well as increased amplitudes of the N170 (Peltola et al., 2018) and the vertex positive potential (VPP; Huffmeijer et al., 2013), indicating enhanced sensitivity and improved neural efficiency to process emotional faces. Yet, results were inconsistent for the late positive potential (LPP): both increased amplitudes (Huffmeijer, 2013), as well as no OXT effects (Peltola, 2018) were reported for this component. However, only few EEG studies have investigated the effects of a single dose of OXT on facial emotion processing, hence, further research is needed to gain more insight in a neural OXT effect.

4. Towards a better understanding of automatic facial expression processing mechanisms

Overall, mapping the differences in facial emotion processing between typically developing individuals and individuals with ASD is hampered by the mixed and inconsistent results, at a behavioural, as well as at a neural level.

Pertaining to the neural level, the classic ERP approach often requires long EEG recordings due to the low signal-to-noise ratio. Moreover, differently selected time windows across ERP studies, as well as the variable timing of the individual brain responses (Kremláček et al., 2016), might hamper the objective markings of the neural response, especially at an individual level. Furthermore, ERPs do not offer a selective categorical response for one type of features or stimuli. In addition, the variation in brain activation might (partially) be explained by the variance within ASD. This entails an additional disadvantage for fMRI studies, as fMRi generally only allows comparisons at a group level.

Hence, a **more sensitive measure** is required to reliably measure emotional face processing abilities, not only at a group level, but also at an **individual subject level**, which allows us to gain more insight into the heterogeneity within the autism spectrum.

In addition, considering the potential confounding influences of mechanisms other than facial expression processing per se, as well as the impact of task demands on explicit emotion recognition, applying **implicit** measures allows us to effectively target **automatic** emotion processing.

4.1 Fast periodic visual stimulation and combined frequency-tagging EEG

Although a series of implicit measures was applied to gain more insight into the automatic facial expression processing mechanisms in typically and atypically developing individuals, this doctoral project is mainly centred around the fast periodic visual stimulation (FPVS) approach in combination with frequency-tagging EEG.

Frequency-tagging EEG is based on the principle that brain activity synchronizes to a periodically flickering stimulus (Adrian & Matthews, 1934). We applied this principle in an oddball paradigm, where we presented images of neutral faces at a fast rate of 6 Hz, periodically interleaved with expressive faces every fifth image (i.e. at 1.2 Hz oddball frequency), allowing us to objectively quantify the neural sensitivity for specific facial expressions. When we apply a fast Fourier transformation on the EEG data and transform the signals from the time domain into the frequency domain, we will see a response at exactly the frequency of the base rate stimulation (here, 6 Hz; Fig.3). If participants are able to discriminate between the base (i.e. neutral faces) and the oddball (i.e. expressive faces) stimuli, in addition to the general synchronization response, we will also see a brain response at exactly the frequency of the oddball presentation (Fig.3).

Indeed, the periodic presentation at these predefined, yet, different, frequency rates generates distinguishable frequency tags for the base and oddball stimuli, allowing direct quantification of the neural responses, indicating the discrimination of expressive faces amongst neutral faces. This makes frequency-tagging EEG a **highly objective measure**. In addition, the rapid presentation rate not only pinpoints **expression processing at a single glance**, but it also enables a **fast** acquisition of many neural responses indexing expression discrimination in only a few minutes of recording, with a **high signal-to-noise ratio**. In addition, FPVS in combination with frequency-tagging EEG allows the collection of robust discriminative responses, not only at a group level, but also at an **individual level**. Finally, as participants typically perform an unrelated orthogonal control task and do not consciously process the presented stimuli, this approach is **unconfounded by task demands** and targets the **automatic and implicit neural processing** of facial emotional information.

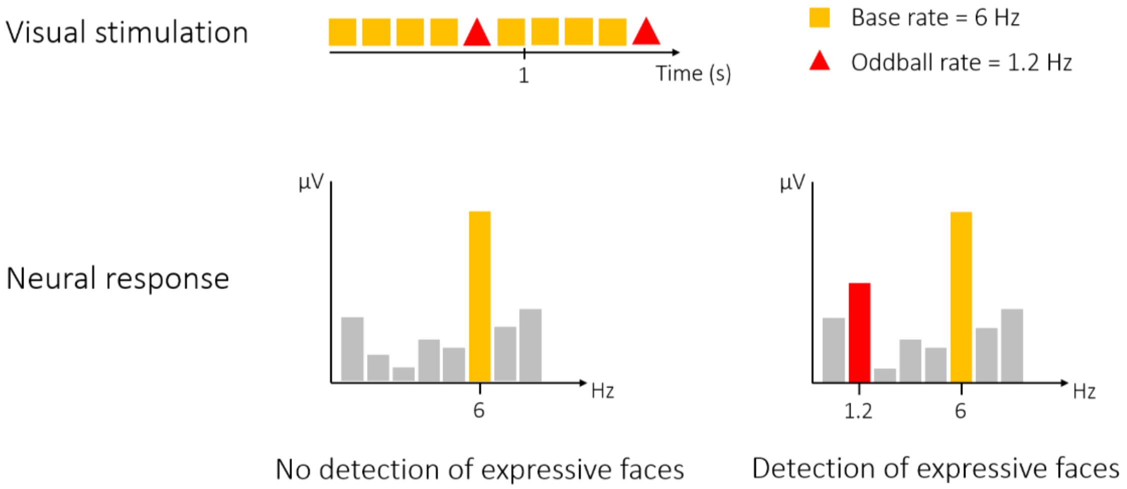

Figure 3. *Principle of frequency-tagging EEG: the brain synchronizes its activity to a periodically flickering stimulus.* ***Upper row****: oddball paradigm where base images (yellow squares) are presented at 6 Hz, periodically interleaved every 5th image with an oddball stimulus (red triangles).* ***Lower row****: neural responses;* ***(left)*** *if participants are unable to detect the oddball images in between the stream of base images, we will only see the general visual base rate response (6 Hz);* ***(right)*** *if participants are able to detect the oddball images in between the stream of base images, then, in addition to the general visual base rate response, we will also see a clear response at exactly the frequency of the oddball stimulation (here: 1.2 Hz).*

5. Aims, outline and potential impact

The general aim of this doctoral project was to thoroughly investigate the automatic facial expression processing mechanisms in typically and atypically developing individuals via a series of implicit and explicit measures. The following five chapters serve three broad objectives to address the overall aim:

1. To pinpoint the threshold of optimal spatial frequency information for the rapid automatic detection of fearful faces in healthy adult participants (chapter 1)
2. To investigate different automatic emotion processing mechanisms in school-aged boys with and without ASD, by means of a series of state-of-the-art approaches (chapter 2-4)
3. To explore the effect of a single dose of oxytocin on the neural sensitivity to expressive faces in healthy adult participants (chapter 5)

Part I. Back to basics

Understanding automatic emotion processing also includes its most basic mechanisms. Therefore, the first part of this doctoral thesis entails the more fundamental study in the search of the minimally required SF information for rapid fear discrimination, both implicit and explicit **(chapter 1)**. Here, we wanted to learn how the basic visual characteristics affect automatic emotional face processing.

Part II. (A)typicalities in facial expression processing

In the second part, we zoom in on the potential differences in the automatic mechanisms underlying emotional face processing in school-aged boys with and without ASD. First, we investigated whether boys with ASD and TD boys differ in their neural sensitivity to rapidly and implicitly process fearful faces **(chapter 2)**. In addition, we wanted to gain more insight into their applied perceptual strategy (i.e. holistic or feature-based) and the most informative facial cue to detect fearful faces. In **chapter 3**, we consolidated and expanded our previous findings by examining whether the reduced neural sensitivity in boys with ASD only applies to fear (i.e. is emotion-specific) or if it generalizes to different basic facial expressions. In addition, we challenged the robustness of the FPVS EEG approach and the social brain even further by investigating expression discrimination across large differences in facial identities. Whereas we investigated information extraction during implicit emotion processing in chapter 2, in **chapter 4**, we focused on the automatically applied visual scanning patterns while explicitly processing emotional faces. In addition, we explored the facial mimicry responses to different facial expressions while recognizing the emotions. Discovering more about the automatic emotion processing mechanisms might allow to understand why specific training may or may not work effectively and how to redirect it if it does not work.

Part III. To sniff or not to sniff?

The last chapter of this doctoral dissertation **(chapter 5)** focuses on the effect of a single dose of the prosocial neuropeptide oxytocin on the neural sensitivity for different facial expressions in healthy adult participants. Given that oxytocin has been found to increase attentional resources for salient social cues (social saliency hypothesis, Shamay-Tsoory, 2016), and attenuates or facilitates the processing of negative versus positive emotional stimuli, respectively (Ellenbogen, 2018), this might be particularly relevant for facial emotion recognition. As such, these results may provide first indications for effective treatment interventions in enhancing the emotional face processing skills of individuals with difficulties on the social domain (e.g. individuals with ASD).

Finally, at the end of this doctoral dissertation, we included a **general discussion** with the summarized main findings of this doctoral project discussed in light of the available literature. Furthermore, we will discuss the anticipated impact of the project, and propose directions for future research.

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Part I

Back to basics

Chapter 1

Pinpointing the optimal spatial frequency range for automatic neural facial fear processing

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Published in *NeuroImage*

(2020), 221. DOI: 10.1016/j.neuroimage.2020.117151

Abstract

Faces convey an assortment of emotional information via low and high spatial frequencies (LSFs and HSFs). However, there is no consensus on the role of particular spatial frequency (SF) information during facial fear processing. Comparison across studies is hampered by the high variability in cut-off values for demarcating the SF spectrum and by differences in task demands. We investigated which SF information is minimally required to rapidly detect briefly presented fearful faces in an implicit and automatic manner, by sweeping through an entire SF range without constraints of predefined cut-offs for LSFs and HSFs. We combined fast periodic visual stimulation with electroencephalography. We presented neutral faces at 6 Hz, periodically interleaved every 5th image with a fearful face, allowing us to quantify an objective neural index of fear discrimination at exactly 1.2 Hz. We started from a stimulus containing either only very low or very high SFs and gradually increased the SF content by adding higher or lower SF information, respectively, to reach the full SF spectrum over the course of 70 seconds. We found that faces require at least SF information higher than 5.93 cycles per image (cpi) to implicitly differentiate fearful from neutral faces. However, exclusive HSF faces, even in a restricted SF range between 94.82 and 189.63 cpi already carry the critical information to extract the emotional expression of the faces.

1. Introduction

Human faces contain a large and varied set of sources of information, conveyed by a spectrum of spatial frequencies (SFs) – i.e. the basic components of visual information, characterized by their spatial distribution of luminance variations (De Valois and De Valois, 1980). This information needs to be extracted fast and efficiently during social interaction in order to be able to act appropriately in every situation (Ruiz-Soler and Beltran, 2006). It has been suggested that the information represented by the various SFs in a face is processed in a coarse-to-fine sequence: the coarse and more global low SF (LSF) information is being processed first, with subsequent processing of the fine and more local higher SFs (HSF), for robust and precise categorization (De Cesarei and Codispoti, 2013; Goffaux et al., 2011; Goffaux and Rossion, 2006; Hegdé, 2008; Quek et al., 2018). However, other authors have argued in favour of a more flexible use of spatial frequencies rather than a fixed one, based on task demands and stimulus properties (de Gardelle and Kouider, 2010; Morrison and Schyns, 2001; Ruiz-Soler and Beltran, 2006; Schyns and Oliva, 1999).

To better understand how the visual system processes faces, several studies have aimed at pinpointing the range of SFs that play the most crucial role in (different aspects of) face processing. Very roughly, SFs < 8cpi can be considered as LSFs, 8 cpi < SFs < 24 cpi as middle-range SFs (MSFs), and SFs > 24 cpi as HSFs (Morrison and Schyns, 2001; Schyns and Oliva, 1999; Vuilleumier et al., 2003; Wang et al., 2015). Some studies emphasize the importance of LSF information for face discrimination or face recognition, suggesting the redundancy of HSF information (Canário et al., 2016; Goffaux et al., 2003a). On the other hand, the importance of both LSF and HSF information for face recognition has also been reported (Fiorentini et al., 1983; Flevaris et al., 2008; Halit et al., 2006). Finally, while either LSFs or HSFs may enable face recognition, the optimal SF range for face recognition has been suggested to comprise MSFs (Collin et al., 2012; Costen et al., 1996; Leonard et al., 2010; Morrison and Schyns, 2001; Ruiz-Soler and Beltran, 2006). This particular tuning of the visual system towards MSFs for face processing, may align with the fact that most physical face information is present in this MSF range, with facial amplitude maxima occurring around 10 cpf, particularly in horizontal orientation (Collin et al., 2014; Keil, 2008).

1.1 Spatial frequencies and emotional face perception

In addition to identity information, faces can also convey an assortment of emotional information. Compared to facial identity recognition, facial emotion recognition requires more details (Gao and Maurer, 2011) and has a greater sensitivity to changes in SF (Goren and Wilson, 2006). Depending on the displayed facial expression, different SF information is preferentially used during processing. For example, when categorizing fearful versus neutral expressions, a LSF bias has been observed, both at the behavioural (Holmes et al., 2005) and at a neural level (Pourtois et al., 2005; Vlamings et al., 2009; Vuilleumier et al., 2003). The LSF bias for behavioural fear categorization has also been demonstrated when compared to faces displaying happiness (Morawetz et al., 2011). However, other studies reported an advantage of HSF information for the detection of fearful versus neutral faces (Stein et al., 2014), and the recognition of fear as opposed to other facial expressions, including anger, happiness and disgust (Smith and Merlusca, 2014). Moreover, as for identity perception, the importance of MSFs has also been demonstrated for expression recognition (Gao and Maurer, 2011).

Overall, and irrespective of the particular emotion being presented, conflicting results have been found on the role of SFs in emotional face processing (for reviews, see De Cesarei and Codispoti, 2013; Jeantet et al., 2018). The methodological variability across studies, in terms of the emotion processes being measured, the methods to modulate the SF availability at the stimulus level, and the experimental parameters (e.g. stimulus size, viewing distance, duration of stimulus presentation), contribute to these inconsistencies (De Cesarei and Codispoti, 2013; Jeantet et al., 2018). In addition, also the behavioural task that is performed may influence the preferential use of specific SFs for (emotional) face processing, as diverse task demands may call for specific diagnostic cues, enveloped in certain SF ranges (Goffaux et al., 2003b; Schyns and Oliva, 1999; Smith and Merlusca, 2014). Furthermore, comparison across studies is also hampered by the use of different units to express the SF content of the stimuli, as well as the use of highly variable cut-off values for demarcating the SF spectrum into LSFs, MSFs or HSFs (Jeantet et al., 2018). To move the field forward, ideally, the role of SF content on facial expression processing should be investigated in an implicit and automatic manner, without particular task demands that may modulate the impact or importance of particular SF content and without predefined and limited SF cut-offs, as explained next.

1.2 Present study

With the present study, we investigate the impact of SF content on the implicit neural detection of fearful faces among a series of rapidly presented neutral faces. We determine the minimally required SF information by systematically sweeping through a low-to-high and high-to-low SF space and employing a fast periodic visual stimulation (FPVS) oddball paradigm in combination with scalp electroencephalography (EEG). As in previous studies (Dzhelyova et al., 2017; Van der Donck et al., 2019), we present neutral faces at a fast periodic rate of 6 Hz, interleaved with expressive faces every 5th image, thus at 1.2 Hz oddball rate (see Fig.1A). Here, we focus on fear detection, because of its evolutionary importance and its potential to elicit large neurophysiological responses (Nuske et al., 2014; Smith, 2012; Van der Donck et al., 2020). The periodic presentation at predefined, yet different, base and oddball frequency rates allows the direct quantification of the implicit neural responses, indicating the discrimination of fearful faces amongst neutral faces. In addition, the rapid presentation of the facial stimuli during this paradigm promotes automatic processing. By combining this implicit neural measure with an additional explicit fear-discrimination task (at the same presentation rate), we can investigate a possible differential use of SF information when processing facial expressions implicitly versus explicitly (Langner et al., 2012; Rohr and Wentura, 2014).

Based on a similar sweep paradigm addressing face categorisation (Quek et al., 2018), we progressively increased the SF content of an image stream during 70 seconds, starting from a face image containing either only LSFs or only HSFs, until reaching the full spectrum with clearly recognizable neutral and fearful faces (see Fig.1B/movies 1 and 2). The progressive changes of the SF filter cut-offs allow us to vary the SF content across a broad range throughout one stimulation sequence, without decomposing the images into discrete SF bands, thereby enabling the quantification of cumulative integration of facial expression information (Quek et al., 2018). Accordingly, this paradigm might allow us to pinpoint the threshold of optimal SF information for the rapid detection of fearful facial expressions, without prior assumptions about SF preferences.

Based on previous studies that demonstrated activity in higher-level face processing regions (e.g. fusiform gyrus) in response to LSF (Canário et al., 2016; Goffaux et al., 2011; Winston et al., 2003) as well as HSF faces (Goffaux et al., 2011; Rotshtein et al., 2007), we generally expect to see most brain activation over the left and right occipito-temporal regions.

As one may wonder to what extent our findings on preferred SF content are specific for facial fear detection and not merely for change detection in general (Morawetz et al., 2011), we added a control experiment where we inverted all the faces. While this manipulation preserves all low-level perceptual features, it has been well documented that face inversion typically disrupts holistic or configural face processing (Rossion, 2013; Tanaka and Farah, 1993; Vettori et al., 2019). Accordingly, we hypothesize that oddball responses will be lower for the inverted as compared to the upright faces. Previous studies have reported inversion effects for facial fear processing using FPVS oddball paradigms with full scale SF images (Dzhelyova et al., 2017; Van der Donck et al., 2019), but the inversion effect has also been observed in SF filtered faces. Most often, this face inversion effect has been reported in LSF faces (Flevaris et al., 2008; Goffaux, 2009; Goffaux and Rossion, 2006; Jeantet et al., 2018), suggesting that LSFs specifically contain the holistic or configural face information (Goffaux et al., 2005). Against this background, and given that HSFs comprise the facial features which are preserved during face inversion, we may expect a larger face inversion effect (i.e. lower fear-discrimination responses for inverted faces) for LSF versus HSF facial images. However, as configural relations between facial features can also be extracted on the basis of exclusive HSF information (Collin et al., 2014; Goffaux et al., 2005), we might also find a significant (but smaller) face inversion effect when only HSF information is present.

2. Methods

2.1 Participants

In the ***main experiment***, twenty right-handed healthy young adults (10 females) aged between 18 and 35 years old (mean age = 21.61 years, *SD* = 1.59) participated. One participant reported colour blindness, yet, because this did not affect the processing of the greyscale facial images or the detection of the colour-changes of the fixation cross, this participant was not excluded. In the ***control experiment***, we included a new group of ten healthy young adults (5 females; mean age = 26.48 years, *SD* = 3.21).

All participants reported normal or corrected-to-normal visual acuity. Given the "own-culture advantage" of emotion processing (Elfenbein & Ambady, 2002; Gendron et al., 2014), participants had to be living in Belgium or Europe for at least 5 years. An exclusion criterion was the diagnosis of epilepsy or autism spectrum disorder in the participant or in a first-degree relative. The Medical Ethical Committee of the university hospital approved this study. Written informed consent according to the Declaration of Helsinki was gathered from the participants prior to participation.

2.2 Stimuli

Full-frontal images of a neutral and fearful face of two male and two female actors were acquired from the Karolinska Directed Emotional Faces (KDEF) database (AF07, AF22, AM05, AM11, (Lundqvist et al., 1998)). Consulting the KDEF ratings, the most expressive faces were chosen in terms of reported arousal and intensity. All images were sized to 450 x 450 pixels and we removed the shoulders and stray hair, made the background transparent and centred the images on the nasion (i.e. the nose bridge). External features (e.g. hair and ears) were not removed, since this did not have an impact on the SF filtering. The stimuli were displayed subtending 6.01° visual angle at 80 cm viewing distance.

The broadband butterworth SF filtering (second order) of the images was performed using Matlab R2017b (The MathWorks, Inc.) and was based on the study of Petras et al. (2019). The full-spectrum neutral and fearful faces were first converted to greyscale and then bandpass filtered (i.e. by multiplying the Fourier amplitude of each image with the chosen SF filters, before transforming the stimuli back into image space) with seven logarithmic cut-offs (i.e. SF steps). This enabled us to investigate an entire range of SFs between 1.48 and 189.63 cpi (corresponding to approximately 0.66 and 84.46 cycles per face width (cpf), based on the mean cut-off estimate across the faces of the four actors). In two separate continua, we started from a stimulus with isolated LSF content or HSF content, where SF information was incrementally added throughout the seven SF steps, towards a stimulus containing the full spectrum (Fig.1B). Henceforth, we will refer to these continua as the LSF-to-HSF continuum and the HSF-to-LSF continuum, respectively.

The resulting spatially filtered greyscale images were placed against a grey background (RGB = 128, 128, 128; alpha = 255) and equalized for contrast and luminance to match the mean values of the full-spectrum images. Consequently, per condition, all images had equal contrast and luminance, both within and across the seven SF steps, to ensure that only the facial expression differed between the base and oddball stimuli.

2.3 Design and procedure

Participants were seated in a dimly lighted room at 80 cm viewing distance of a LCD 24-in. computer screen. A custom application software written in Java was used to display the stimuli through square wave presentation, because the display time of the full contrast stimulus is much longer with a square wave presentation than sinusoidal contrast modulation. The 100% contrast stimulus presentation was approximately 167 milliseconds (see Fig.1A). To avoid detection of the fearful face due to low-level repetition effects, the stimuli varied randomly in size between 80% and 120% of the original size.

To guarantee attentiveness of the participants, an orthogonal task was implemented. A fixation cross, presented on the nasion of the face, briefly (300 ms) changed color from black to red 10 times within every sequence. The participants had to press a button as soon and accurately as possible when noticing the color changes of the fixation cross.

2.3.1 Implicit fear discrimination

In the ***main experiment***, the fear detection sweep paradigm consisted of 32 sequences in a randomized order with a sequence duration of 70 seconds. SF information was progressively added in seven logarithmic steps (10 seconds per SF step) within one sequence towards a stimulus containing the full SF-spectrum of 1.48 – 189.63 cpi (Fig.1B). In the LSF-to-HSF continuum, the sequences started with a stimulus exclusively encompassing LSF information and each SF step added supplemental higher SF information. In contrast, the sequences of the HSF-to-LSF continuum started with a stimulus solely containing HSF information, adding lower SF information with each SF step. The sequence started and ended with a pre- and postlude step that functioned as a fade-in and a fade-out. This gradual start and end of each sequence was implemented to minimize artefacts due to the stimuli appearing or disappearing abruptly.

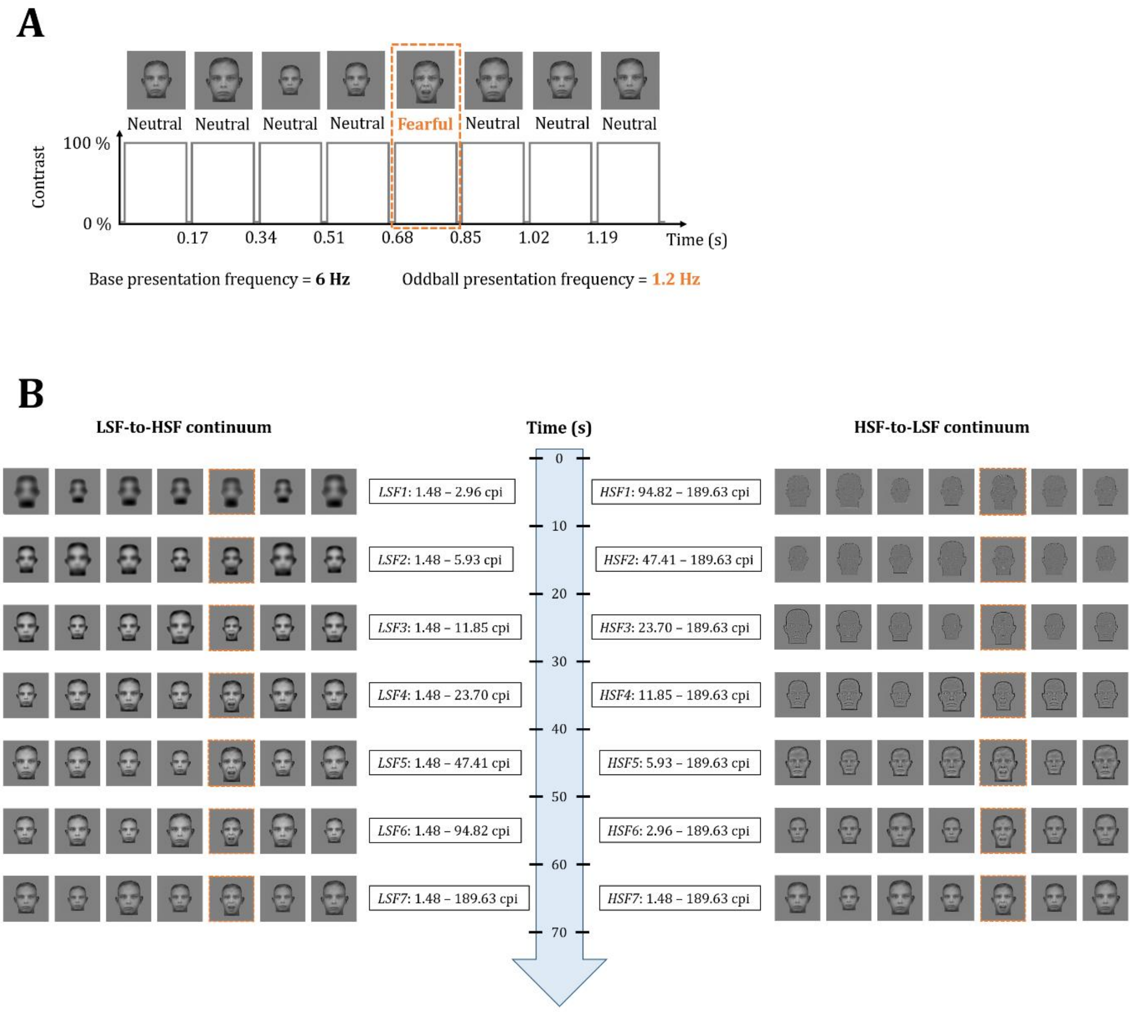

Figure 1. A. Visualization of the square wave presentation of the experimental stimuli for a full SF spectrum face (i.e. SF 7). The stimulus sequence presented in each SF step: four neutral faces (base stimulus), followed by a fearful face (oddball stimulus). The base and oddball stimuli only differ in terms of facial expression; their SF content is identical. The placement of the fixation cross is not visualized. B. Examples of the seven logarithmic SF steps of the LSF-to-HSF and the HSF-to-LSF continua. Each SF step comprises 10 s of stimulus presentation, i.e. neutral faces periodically interleaved with fearful faces (every 5th image, i.e. 1.2 Hz). The stimuli of SF step 7 in both continua are identical, as they encompass the same SF range of 1.48 – 189.63 cpi. The original images were acquired from the KDEF database (Lundqvist et al., 1998) and adapted for experimental purposes.

The 32 sequences comprised 16 LSF-to-HSF sequences (4 for each facial identity) and 16 HSF-to-LSF sequences (4 for each facial identity). This implies that every SF stimulus step was presented 16 times during a 10s segment, totalling up to 160 s stimulation time, which is identical to the stimulation time used in previous (non-sweep) FPVS fear detection oddball paradigms (Dzhelyova et al., 2017; Van der Donck et al., 2019).

Within each sequence and within each SF step, neutral faces of one individual are presented at a base rate frequency of 6 Hz, periodically interleaved every fifth stimulus with a fearful face (oddball frequency of 1.2 Hz, i.e. 6 Hz/5) of the same individual. The only difference between the base (neutral faces) and oddball (fearful faces) stimuli is the facial expression; the SF content of the base and the oddball stimuli are identical (Fig.1B). All images are presented upright.

In the ***control experiment***, we implemented a control condition where we, in addition to the sequences with the upright faces, also presented sequences with inverted faces. All other experimental parameters remained identical to the main experiment. Given that the main experiment showed that reliable fear-discrimination responses could already be obtained with half the number of stimulation sequences (i.e. 8 LSF-to-HSF and 8 HSF-to-LSF sequences), the control experiment only comprised 8 sequences per condition, resulting again in 32 sequences in total (based on both SF-continua and both orientations of the faces).

2.3.2 Explicit fear discrimination

Task demands have been found to modulate the use of particular SF information to enable fast stimulus processing (Awasthi et al., 2011; De Cesarei and Codispoti, 2013), while spontaneous SF processing without a specific visual task may shed light on the default SF components involved in implicit emotional face detection (Ruiz-Soler and Beltran, 2006). To investigate the mapping between implicit and explicit fear discrimination thresholds, we also administered an explicit behavioural fear detection task at the end of the test session.

For this task, again two sequences of the aforementioned fear detection sweep paradigm were shown: one sequence of the LSF-to-HSF continuum and one sequence of the HSF-to-LSF continuum, both displaying an individual of the same gender. Sequences displaying males or females were alternated for every participant. Here, participants had to press the response button once per sequence as soon as they detected a face with a fearful expression. Images were presented without a fixation cross, allowing the participants to look anywhere they wished on the computer screen.

2.4 EEG acquisition

We recorded EEG activity using a BIOSEMI Active-Two amplifier system with 64 Ag/AgCl electrodes and two additional electrodes as reference and ground electrodes (Common Mode Sense active electrode and Driven Right Leg passive electrode). Vertical eye movements were recorded via one electrode above and one below the right eye. One electrode was placed at the corner of both eyes to record horizontal eye movements. We recorded EEG and electrooculogram at 512 Hz. The electrode offset was kept under 30 µV.

2.5 EEG data analysis

Preprocessing. Similar to Quek and colleagues (2018), we processed all EEG data using Letswave 6 (http://www.nocions.org/letswave/) in Matlab R2017b (The Mathworks, Inc.). We cropped the data into segments of 75 seconds (3 s before and 2 s after each sequence), applied a fourth-order Butterworth bandpass filter (0.1-100 Hz) and resampled the data to 256 Hz. For four participants who blinked on average more than 15 times (based on robust Z-scores > 2.5 (Rousseeuw and Hubert, 2018)) within one sequence, we applied independent component analysis via the runica algorithm (Makeig et al., 1995) and removed the component that accounted for most of the variance. We re-estimated noisy or artifact-ridden channels through linear interpolation of the three spatially nearest, neighboring electrodes; on average across all participants, 1.42 electrodes were interpolated. All data segments were re-referenced to a common average reference and we averaged each participant's sequences for the LSF-to-HSF and HSF-to-LSF continua separately. The preprocessed data segments were then cropped according to each SF step (7 x 10 s segments).

Frequency-domain processing. Then, a fast Fourier transformation (FFT) was applied, yielding a spectrum between 0 and 127.84 Hz with a spectral resolution of 0.1 (=1/10s). In addition to the signal at the oddball and base frequencies, signals at frequencies corresponding to integer multiples (harmonics) of these base and oddball frequencies are also present in the spectrum. Only the amplitudes at the oddball frequency and its harmonics (i.e. n*F/5 = 2.4 Hz, 3.6 Hz, etc.) are considered as an index of facial expression discrimination (Dzhelyova et al., 2017). We used signal-to-noise ratio (SNR) and baseline-corrected amplitudes to describe these measures. SNR is calculated by dividing the amplitude value of a specific frequency bin by the average amplitude of the 8 surrounding frequency bins (Rossion et al., 2012). Baseline-corrected amplitudes are calculated by subtracting the average amplitude level of the 8 surrounding bins from the amplitude of the frequency bin of interest (Retter & Rossion, 2016). For both measures, these 8 surrounding bins are the 4 bins on each side of the target frequency bin, excluding the immediately neighbouring bins and the two bins with the most extreme values, corresponding to a frequency range of 0.4 Hz. We used SNR spectra for visualization (see Fig.2) because responses at high frequency ranges may be of small amplitude, but with a high SNR. Baseline correction expresses responses in amplitudes (µV) that can be summed across significant harmonics to quantify the overall base and oddball response (Retter & Rossion, 2016).

To estimate the number of informative oddball harmonics, we assessed the significance of the responses at different harmonics by calculating Z-scores – using the mean and standard deviation of the 8 frequency bins surrounding the bin of interest (Liu-Shuang et al., 2014) – on the FFT grand-averaged data across all electrodes and across electrodes in the relevant regions of interest (ROIs; cf. infra). Harmonics were considered significant and relevant to include as long as the Z-score for two consecutive harmonics was above 1.64 ($p < .05$, one-tailed) (Retter and Rossion, 2016). Following this principle, we quantified the oddball responses of the main and the control experiment as the sum of the oddball harmonics until the sixth harmonic following the first harmonic (i.e. 1.2 Hz), and the first four harmonics, respectively, excluding the harmonics corresponding to the base rate frequency.

Determination of ROIs. Visual inspection of the topographical maps and identification of the most responsive regions for emotional oddball stimulation (Dzhelyova et al., 2017; Van der Donck et al., 2019) led to three ROIs, identical for all paradigms. The left and right occipito-temporal (LOT and ROT) ROI were defined by averaging for each hemisphere the three channels with the highest summed baseline-corrected oddball response (i.e. channels P7, P9 and PO7 for LOT, and P8, P10 and PO8 for ROT). The medial-occipital ROI (MO) was defined by averaging the four channels with the largest common response at 6 Hz (i.e. channels Iz, Oz, O1 and O2).

2.6 Statistical data analysis

For statistical analyses of the baseline-corrected oddball amplitudes in each ROI, we applied a linear mixed-model (LMM) (function 'lmer' in R (Bates et al., 2015)), fitted with maximum likelihood. For both the main and the control experiment, a LMM was applied to the two SF conditions (LSF-to-HSF and HSF-to-LSF continua) separately, because main or

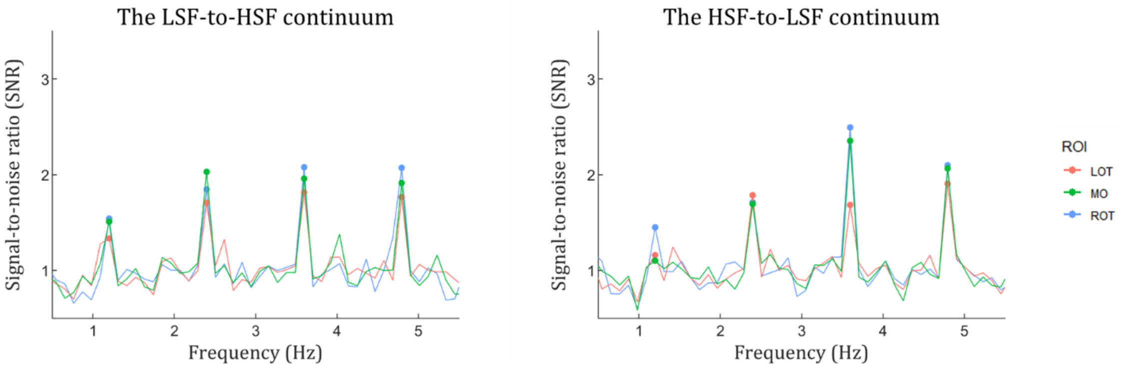

Figure 2. SNR-spectra visualizing the fear-discrimination responses during SF step 7 in both continua, for the three ROIs separately. The significant first four harmonics are displayed.

interaction effects with this factor would not be of interest given the nature of the filtering parameters (Watier et al., 2010). *SF content* (seven SF steps) and *ROI* (LOT, ROT and MO) were included as fixed within-subject factors and a random intercept per participant to account for repeated testing. For the analysis of the control experiment, also *Orientation* (upright versus inverted) was included as a fixed within-subject factor. Degrees of freedom were calculated using the Kenward-Roger method. Posthoc contrasts were tested for significance using a Bonferroni correction for multiple comparisons, by multiplying the p-values by the number of comparisons. Cohen's *d* effect sizes were calculated by dividing the least square means difference by the pooled standard deviation. All assumptions in terms of linearity, normality and constant variance of residuals were verified and met for all LMMs.

For all analyses with EEG data, extreme outlying data points (based on a Cook's distance of more than six times the mean) were removed (Christensen et al., 1992). For one participant from the main experiment, data collection only included the LSF-to-HSF continuum. Consequently, analyses for the sweep FPVS oddball paradigm of the main experiment were conducted with data from 20 and 19 participants for the LSF-to-HSF continuum and HSF-to-LSF continuum, respectively.

Finally, a LMM was applied to ensure that the base and oddball responses for upright faces in the main and control experiment would not differ significantly, hence, indicating that the results in the control experiment can only be attributed to the orientation of the presented faces and not to underlying differences in this sample's response to upright faces.

For the behavioural data of the orthogonal task, we performed a Mann-Whitney U test.

17 of the 20 participants included in the main experiment performed the explicit behavioural task. Due to a missing value from one participant in each SF continuum, the data from 16 participants were analysed in both continua.

2.6.1 Fear detection threshold

As we aimed at pinpointing a neural detection threshold for the rapid discrimination of fearful faces amongst neutral faces, we evaluated the amount of SF content necessary for significant fear detection by calculating the 95% confidence interval around the group average fear-discrimination amplitude at each SF step (Quek et al., 2018). We interpreted the first SF step where the 95% confidence interval did not include zero as the fear-detection threshold, that is, the step where the discrimination response first emerged.

For the explicit fear discrimination task, we considered the SF step where at least half of the participants could detect the fearful face (i.e. the median value) as the most crucial cross-over point for behavioural fear detection.

3. Results

3.1 Explicit behavioural task

Figure 3 provides a histogram displaying the number of participants that detected the fearful expression for each of the SF levels along the LSF-to-HSF and the HSF-to-LSF continuum. For the LSF-to-HSF continuum, the median detection level is situated at 3.5, which comprises SF3 and SF4 (max. range: 1.48 to 23.70 cpi, or 0.66 to 10.56 cpf). For the HSF-to-LSF continuum, the median of SF2 (SF range: 47.41 to 189.63 cpi, or 21.12 to 84.46 cpf) indicates that these images contained sufficient information to report detection of fearful faces.

3.2 Fixation cross change detection tasks

Results of the colour change detection tasks suggest similar levels of motivation and attention to the screen throughout both the main and the control experiment, across both continua and across upright and inverted faces, with equal accuracies (all $p > .22$) and reaction times (all $p > .44$) for all these conditions.

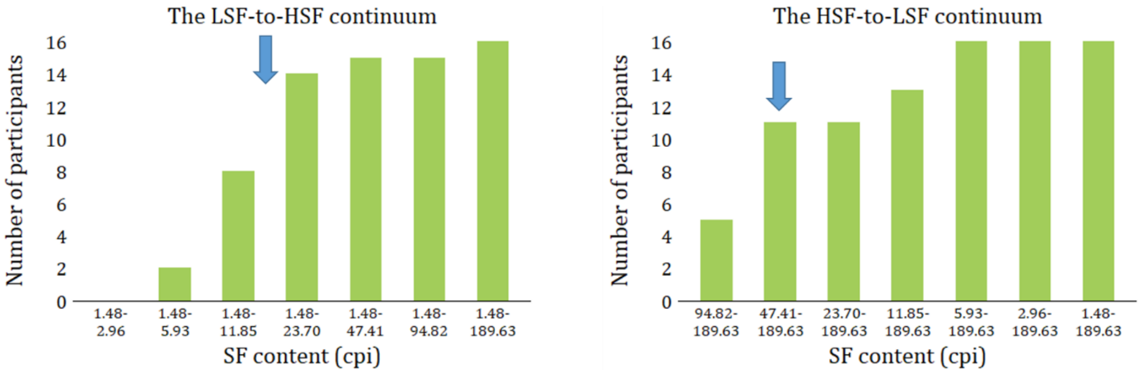

Figure 3. *The cumulative number of participants that explicitly detected the fearful expression for each of the SF levels along the LSF-to-HSF and the HSF-to-LSF continuum.*

3.3 Fear-discrimination responses main experiment

The implicit, neural fear-discrimination responses, averaged across all participants, are visualized per SF step in Figure 4.

3.3.1 LSF-to-HSF continuum

The LMM demonstrated a significant main effect of *SF content* (F(6, 367) = 45.07, p < .0001), with a significantly higher fear-discrimination response for LSF4 (M_{LSF4} = 0.19 µV) versus LSF2-3 (M_{LSF2} = -0.02 µV, M_{LSF3} = 0.07 µV; $t(367)_{LSF2\text{-}LSF4}$ = -5.47, d = -1,14; $t(367)_{LSF3\text{-}LSF4}$ = -3.16, d = -0.59; all $p_{Bonferroni}$ < .05) and for LSF5-6-7 (M_{LSF5} = 0.35 µV, M_{LSF6} = 0.45 µV, M_{LSF7} = 0.43 µV) versus LSF1-2-3-4 (M_{LSF1} = 0.09 µV; $t(367)_{LSF1\text{-}LSF5}$ = -6.40, d = -1.18; $t(367)_{LSF2\text{-}LSF5}$ = -9.31, d = -1.72; $t(367)_{LSF3\text{-}LSF5}$ = -7.01, d = -1.19; $t(367)_{LSF4\text{-}LSF5}$ = -3.88, d = -0.62; $t(367)_{LSF1\text{-}LSF6}$ = -9.10, d = -1.52; $t(367)_{LSF2\text{-}LSF6}$ = -12.01, d = -2.00; $t(367)_{LSF3\text{-}LSF6}$ = -9.69, d = -1.51; $t(367)_{LSF4\text{-}LSF6}$ = -6.56, d = -0.97; $t(367)_{LSF1\text{-}LSF7}$ = -8.51, d = -1.38; $t(367)_{LSF2\text{-}LSF7}$ = -11.39, d = -1.86; $t(367)_{LSF3\text{-}LSF7}$ = -9.09, d = -1.39; $t(367)_{LSF4\text{-}LSF7}$ = -6, d = -0.87; all $p_{Bonferroni} \leq .01$). No other main or interaction effects were present (all p > .08, all d < 0.17).

3.3.2 HSF-to-LSF continuum

The LMM resulted in significant main effects of *SF content* (F(6,352) = 2.50, p < .05) and *ROI* (F(2, 352) = 48.22, p < .0001). Post hoc pairwise comparisons revealed highest responses in the MO compared to the LOT and ROT region, and significantly higher responses in the ROT versus LOT region (M_{MO} = 0.59 µV > M_{ROT} = 0.38 µV > M_{LOT} = 0.28 µV; $t(352)_{LOT\text{-}MO}$ = -9.66, d = 0.96; $t(352)_{LOT\text{-}ROT}$ = -3.23, d = 0.36; $t(352)_{MO\text{-}ROT}$ = 56.32, d = 0.66; all $p_{Bonferroni} \leq .01$). In addition, we found a significantly lower fear discrimination response in HSF5 (M_{HSF5} = 0.33 µV), compared to HSF2 (M_{HSF2} = 0.48 µV; t(352) = 3.11, *d* = 0.44, *p* < .05). The interaction effect between these two factors was not significant (*p* = .18). All *d* for the non-significant findings were < 0.34.

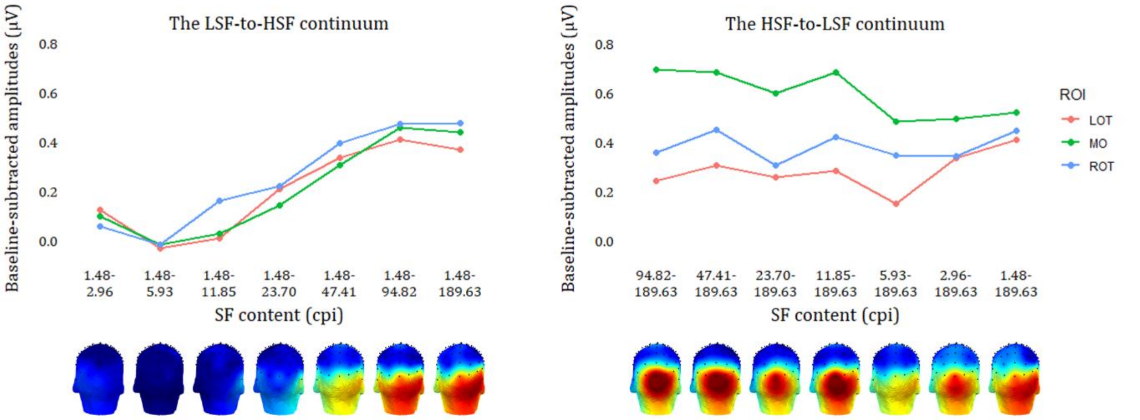

Figure 4. *Fear-discrimination responses for both continua during the main experiment, represented by the three identified ROIs (left and right occipito-temporal (LOT and ROT) and medial-occipital (MO) regions), with the corresponding topographies averaged across all participants.*

3.4 Fear-discrimination control experiment with upright and inverted faces

Figure 5 visualizes the implicit, neural fear-discrimination responses from the control experiment per SF step, averaged across all participants.

3.4.1 LSF-to-HSF continuum

The significant main effect of *Orientation* indicated higher fear-discrimination responses to upright ($M_{upright}$ = 0.20 µV) versus inverted faces ($M_{inverted}$ = 0.05 µV; F(1,355) = 14.31, *p* = .0002). This main effect, and the main effect of *SF content* (F(6,355) = 9.68, *p* < .0001), were further qualified by their interaction (F(6,355) = 2.47, *p* < .05). For the upright faces, higher responses were elicited in LSF5-6-7 (M_{LSF5} = 0.36 µV, M_{LSF6} = 0.49 µV, M_{LSF7} = 0.46 µV) versus LSF1-2 (M_{LSF1} = -0.11 µV, M_{LSF2} = -0.006 µV; $t(355)_{LSF1\text{-}LSF5}$ = -4.32, *d* = -1.08; $t(355)_{LSF2\text{-}LSF5}$ = -3.35, *d* = -0.79; $t(356)_{LSF1\text{-}LSF6}$ = -5.17, *d* = -1.53; $t(356)_{LSF2\text{-}LSF6}$ = -4.27, *d* = -1.17; $t(355)_{LSF1\text{-}LSF7}$ = -5.19, *d* = -1.28; $t(355)_{LSF2\text{-}LSF7}$ = -4.23, *d* = -0.98; all $p_{Bonferroni}$ < .05). Note that these findings are largely similar as in the main experiment with upright faces only. Yet, for the inverted faces there were no differences in response amplitude between stimulus pairs with different SF content (all *p* > .09, all *d* ranging between -0.23 and 0.14). In addition, the inversion effect (i.e. upright versus inverted face contrast) was only present for the HSF faces (i.e. LSF5-6-7, $p_{uncorrected} \leq .05$) and not for the LSF faces. There was no significant main effect of ROI, nor were there interactions with ROI (all *p* > .43, all *d* ranged between -0.13 and 0.13).

3.4.2 HSF-to-LSF continuum

For the data recorded during the control experiment, most importantly, we found a significant main effect of *Orientation* (F(1,360) = 14.60, *p* = .0002) showing that upright faces (M_{upright} = 0.37 µV) elicited larger fear-discrimination responses than the inverted faces (M_{inverted} = 0.20 µV, *d* = 0.35). Furthermore, the significant main effect of *SF content* (F(6,360) = 2.65, *p* < .05) indicated higher oddball responses for HSF1 versus HSF3 (M_{HSF1} = 0.45 µV, M_{HSF3} = 0.14 µV; t(360) = 3.72, *d* = 0.68, *p* < .01). Finally, we found significantly higher responses in the MO region versus the LOT and ROT region (M_{MO} = 0.41 µV, M_{LOT} = 0.18 µV, M_{ROT} = 0.27 µV; $t(360)_{\text{Mo-LOT}}$ = -4.52, *d* = 0.49; $t(360)_{\text{MO-ROT}}$ = 2.80, *d* = 0.32; all $p_{Bonferroni}$ < .05). There were no significant interaction effects (all *p* > .14, all *d* < 0.45).

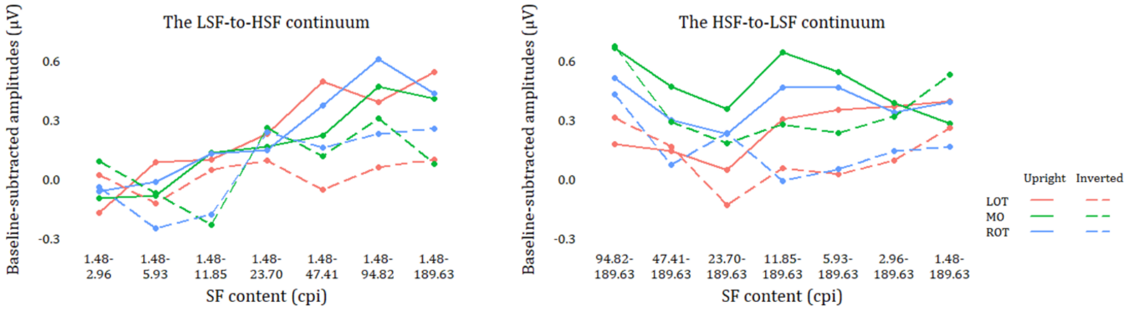

Figure 5. Fear-discrimination responses for both continua during the control experiment, represented by the three identified ROIs (left and right occipito-temporal (LOT and ROT) and medial-occipital (MO) regions).

3.5 Determining the minimally required SF content for implicit neural fear-detection

We conducted two LMMs to investigate whether we could reliably pool the upright face data across the main and control experiment. Most importantly, for neither of both continua was there a main effect nor interaction effect with *Experiment* (*p* > .50, all *d* < 0.13), indicating the similarity of the upright fear-discrimination responses across both participant groups and confirming that data could reliably be combined for further analyses. Further, as expected, for the LSF-to-HSF continuum, there was the same main effect of *SF content* (F(6,560) = 3.39, *p* = .003) as described above. Similarly, for the HSF-to-LSF continuum, there was again the significant main effect of *ROI* (F(2,549) = 8.82, *p* = .0002), showing that highest responses were elicited over the MO region and lowest responses over the LOT region. No other main or interaction effects were significant, in neither of the LMMs (all *p* > .05).

Given that there are no significant differences between the fear-discrimination responses for upright faces in both experiments, we combined the results to increase the power for the identification of the fear-detection threshold. As displayed in Figure 6, the fear-discrimination response almost linearly increased when systematically adding higher SF information to low SF images. The first SF step in the LSF-to-HSF continuum at which the average neural oddball response significantly differed from zero (i.e. the fear-detection threshold, defined as a 95% confidence interval that does not include zero), was located at LSF3 for the ROT region (i.e. 1.48 to 11.85 cpi, or 0.66 to 5.28 cpf) and at LSF4 for the LOT and MO regions (i.e. 1.48 to 23.70 cpi, or 0.66 to 10.56 cpf) (Figure 6). Notably, for the inverted faces, none of the SF steps did reach the fear detection threshold level. When looking at the HSF-to-LSF continuum, on the other hand, we found that the first step with only the highest SF information already elicited clear oddball responses across the three ROIs and that increasing SF information by adding lower SFs did not enhance the responses. As is also evident from Figure 6, indeed, the fear-discrimination threshold can already clearly be identified at HSF1 for all ROIs, indicating that the SF range of 94.82 to 189.63 cpi (or 42.23 to 84.46 cpf) already contains sufficient information to rapidly discriminate fearful faces from neutral faces.

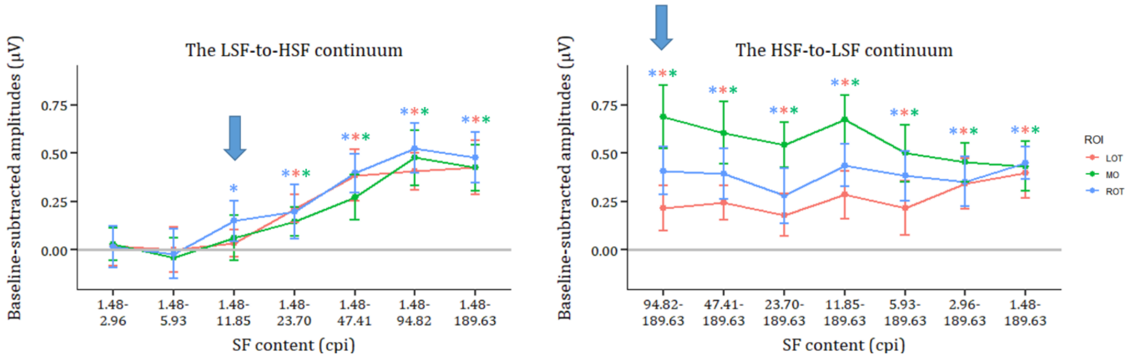

*Figure 6. Pinpointing the implicit neural fear-detection threshold across both SF continua, based on the 95% confidence interval around the mean amplitudes for each SF step. Left: In the LSF-to-HSF continuum, the fearful faces elicit significant neural responses in the ROT region at LSF3 (range: 1.48 – 11.85 cpi) and also in the MO and LOT regions at LSF4 (1.48 – 23.70 cpi). Right: In the HSF-to-LSF continuum, even HSF1 containing only HSFs (range: 94.82 – 189.63 cpi) already displays enough information to elicit significant fear-discrimination responses in each of the three ROIs. * indicate significant neural responses per ROI.*

4. Discussion

Against the background of a highly inconsistent and methodologically variable research field (Jeantet et al., 2018), we applied a FPVS sweep EEG paradigm to evaluate the optimal SF range to rapidly detect fearful faces. By systematically sweeping through an entire SF range, we explored which SF information is minimally required for the brain to detect briefly presented fearful expressions, without being constrained to predefined cut-offs for LSFs and HSFs.

4.1 Implicit neural fear discrimination mainly relies on HSFs

Although a LSF bias has been found for the categorization of fearful expressions (Pourtois et al., 2005; Vlamings et al., 2009; Vuilleumier et al., 2003), our results indicate a key role for HSFs during implicit neural fear discrimination. This is in line with previous research designating fear as a proximal expression that mostly employs higher SFs (Smith & Schyns, 2009). Our EEG data show that, indeed, automatic discrimination between neutral and fearful faces is impaired for LSF-filtered faces, compared to faces containing medium or higher SFs (Goren and Wilson, 2006). This echoes previous findings pinpointing the middle-to-high SF range as optimal for the processing of static expressions (Gao and Maurer, 2011; Plouffe-Demers et al., 2019; Stein et al., 2014). The detection threshold indicates that fearful faces need to comprise at least SF information between 1.48 and 11.85 cpi – corresponding with an SF range between 0.66 and 5.28 cpf – to be rapidly processed in terms of expression and to differentiate fearful from neutral faces. Further adding higher SFs to a LSF face has a significant impact on the implicit neural sensitivity for rapidly presented fearful faces: it leads to an almost linear increase in the amplitude of the fear-discrimination responses. Moreover, the amplitude of the fear-discrimination response keeps increasing when adding higher SFs, even after reaching the initial detection threshold (i.e. the minimally required SF content to elicit a significant fear discrimination oddball response), possibly reaching a saturation plateau around LSF6-7 (cpi > 94.82, or cpf > 42.23), as the signal does not further increase. Possibly, this continuous accumulation of relevant higher SF information allows to progressively generate a (more accurate) visual representation of a fearful face, with its highly defined facial features and configural structure (Quek et al., 2018; Rotshtein et al., 2007), which facilitates the perceptual encoding. The right fusiform gyrus, involving the right fusiform face area, might play a key role in this process: it has been suggested that, here, LSF and HSF information received from separate cortical visual pathways is merged (Rotshtein et al., 2007). Although no exact source localization has been accomplished, it is notable that the ROT region is the first region to signal a significant fear detection threshold. Thus, the fear-discrimination responses in the ROT region were elicited already based on coarser information (LSF3) than those in the LOT and MO region (LSF4).

One may wonder to what extent our paradigm is effectively quantifying sensitivity for fearful expressions and not merely sensitivity to subtle featural perceptual changes. In this regard, it is important to emphasize that the oddball responses are robust despite the presence of continuous changes in stimulus size, thus they are not merely the result of low-level adaptation processes. More importantly, above all, the LSF-to-HSF continuum displays a significant Orientation x SF content interaction, indicating that the systematic increase in oddball responses as a result of adding more HSF content is only evident for the condition with the upright faces and not for the condition with the inverted faces. At the stimulus level, apart from being vertically flipped, low level features of the upright and inverted faces are identical, thus, apparently, they only differ at a perceptual level, with the upright faces being processed in a more configural manner, which increases the sensitivity for high-level facial expression differences. In a similar vein, comparing the significance of the fear detection thresholds in the upright versus inverted condition indicates that the face inversion effect is only present for stimuli comprising MSF to HSF information (i.e. only the MSF and HSF upright faces do show robust oddball fear discrimination responses). Previous studies, however, mostly reported detrimental inversion effects for faces containing only LSFs (Flevaris et al., 2008; Goffaux and Rossion, 2006; Jeantet et al., 2018), thereby suggesting that LSF faces may yield more configural information, which can be disturbed by the inversion operation. More recent studies, however, also reported face inversion effects across a wider range of SFs, including HSF faces (Gaspar et al., 2008; Royer et al., 2017; Willenbockel et al., 2010), thereby corroborating our findings.

Our EEG results contrast with the widespread notion that the processing of evolutionary relevant fearful faces may be driven by a fast subcortical process mainly making use of LSF visual information (Johnson, 2005), yet, it should not surprise that LSFs do not allow automatic fear detection with our oddball paradigm. Indeed, more recent studies have also cited the importance of HSF information in both the cortical and subcortical route for (rapid) fear processing (McFadyen et al., 2017; Pessoa and Adolphs, 2010; Stein et al., 2014).

Indeed, whereas images containing only LSFs did not enable successful discrimination of fearful faces among neutral faces, the results from the HSF-to-LSF continuum indicate that exclusive HSF faces, even in a restricted SF range between 94.82 and 189.63 cpi (i.e. HSF1; corresponding to 42.23 and 84.46 cpf), suffice to generate maximal fear-discrimination responses (as visualized in Figure 6). This is in line with HSFs carrying more detailed and richer information than LSFs (Goffaux et al., 2005), and indicates that HSF1 already carries the critical information to extract the emotional expression of the faces (McBain et al., 2012; Quek et al., 2018). In fact, HSF1 may already carry *all* essential perceptual information to decode the emotional content of the stimulus, as adding lower SF information to the HSF images does not further boost the saliency of the oddball signal. Taken together across both continua, our results indicate that HSF information improves implicit fear discrimination when added to LSFs, and that HSF information by itself is sufficient to rapidly discriminate fearful faces. The presence of a significant inversion effect, also along the HSF-to-LSF continuum, ensures that the neural detection of the fearful faces is not merely driven by sensitivity to low-level perceptual changes. However, inspection of the response patterns for the HSF-to-LSF continuum suggests that these responses may be driven more strongly by basic stimulus characteristics. First, because the topographical distribution of the fear-discrimination responses is mainly centred around the MO region and is less lateralized towards face-selective ROT and LOT regions. Yet, this mostly medially activated topographical pattern for HSFs is in line with previous studies showing stronger activation in the MO region for stimuli containing higher SF information (Hemptinne et al., 2018; Henriksson et al., 2008; Tsuruhara et al., 2013) and suggests the extraction of basic visual properties of facial emotion expressions (Meaux and Vuilleumier, 2016). It seems as if the stimulus properties of HSF1 perfectly match with the tuning of neurons in the primary visual cortex (i.e. preference for higher SFs (e.g. Farivar, Clavagnier, Hansen, Thompson, & Hess, 2017; Sasaki et al., 2001; Singh, Smith, & Greenlee, 2000)), and adding lower SF information immediately results in a reduction of this match (Shapley and Lennie, 1985) and consequently the oddball response, especially for the inverted faces. Second, because especially for HSF1, the face inversion effect is absent, suggesting that these fear detection responses are caused by low-level stimulus characteristics. However, facial emotion recognition has been found to rely on both local features and their global configuration, with varying roles of analytic and holistic information depending on the available information (Meaux and Vuilleumier, 2016; Tanaka et al., 2012). In addition, the visual system has been demonstrated to attend to the most informative scale (Schyns and Oliva, 1999; Sowden et al., 2003). Stimuli in HSF1 only contained very high SFs, hence, being the only informative scale that could be used, and in view of the EEG results, this edge-based information seemed to capture the structure of the facial cues that enable fear detection.

4.2 Explicit fear discrimination relies on a broader SF band

According to the flexible usage theory, the diagnostic SF information invoked for carrying out particular processes is dependent on the particular task demands (Morrison and Schyns, 2001; Oliva and Schyns, 1997; Ruiz-Soler and Beltran, 2006; Smith and Merlusca, 2014). Our results seem to support this. While the emotional expression of the faces can be detected based on a subset of SFs (De Cesarei and Codispoti, 2013), the diagnostic SF information differs slightly dependent whether fearful faces have to be discriminated implicitly versus explicitly. Analyses of the behavioural responses demonstrated that for the majority of the participants explicit fear discrimination emerged around LSF4 and HSF2, whereas the implicit fear-discrimination threshold was located one SF step earlier at LSF3 and HSF1, respectively. This indicates that explicit fear processing seems to require (a little bit) more SF information than the implicit neural encoding of fearful faces. By cumulatively increasing SF information in images containing either only low or only high SFs, the SF range is stretched towards the mid-SF band. Indeed, the mid-SF band, which carries both configural and featural information (Watier et al., 2010), has been found to be optimal for facial expression processing at the behavioural level (Gao and Maurer, 2011; Plouffe-Demers et al., 2019). Possibly, to decide with certainty whether fearful faces are really perceived, participants rely on a broader SF range that increases the visibility of the oddball stimuli.

The main objective of this study was to determine the minimally required SF information (i.e. identifying a detection threshold) for the rapid discrimination of fearful expressions in a series of neutral faces. However, given that the diagnostic information underlying facial expression categorization depends on the comparison categories (Smith and Merlusca, 2014), contrasting a given expression (other than fear) to neutrality or other facial expressions via this sweep FPVS oddball approach would be interesting. In addition, in order to reach our main objective, we equalized the contrast and luminance of the images both within and across the seven SF steps, to ensure that only the facial expression differed between the base and oddball stimuli. Contrast equalization alters the relative contrast of neutral and fearful facial stimuli (Webb and Hibbard, 2019), especially in HSF filtered images (Webb et al., preprint), which might have enhanced the energy of the HSFs. However, as previous findings indicated a LSF bias for fear processing, both in images with and without equalized contrast, despite a faster processing of HSF filtered fearful faces after contrast equalization, as compared to non-equalized images (Vlamings et al., 2009), we believe that our choices of filtering procedure did not inflate the importance of HSF information.

5. Conclusions

We applied a sweep FPVS oddball paradigm to investigate the minimally required SF information for rapid neural and behavioral fear discrimination. Results suggest that rapid and implicit fear detection mainly requires HSF information: HSFs have an additive beneficial value when added to images containing only LSF and HSF information by itself allows neural detection of fearful faces. However, a slightly broader SF range is involved in explicit fear detection. This suggests that rapid fear discrimination mainly relies on the optimal range of middle-to-high SFs.

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Part II

(A)typicalities in facial expression processing

Chapter 2

Fast periodic visual stimulation EEG reveals reduced neural sensitivity to fearful faces in children with autism

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Published in *Journal of Autism and Developmental Disorders*
(2019) 49(11). DOI: 10.1007/s10803-019-04172-0

Abstract

We objectively quantified the neural sensitivity of school-aged boys with and without autism spectrum disorder (ASD) to detect briefly presented fearful expressions by combining fast periodic visual stimulation with frequency-tagging electroencephalography. Images of neutral faces were presented at 6 Hz, periodically interleaved with fearful expressions at 1.2 Hz oddball rate. While both groups equally display the face inversion effect and mainly rely on information from the mouth to detect fearful expressions, boys with ASD generally show reduced neural responses to rapid changes in expression. At an individual level, fear discrimination responses predict clinical status with an 83% accuracy. This implicit and straightforward approach identifies subtle deficits that remain concealed in behavioural tasks, thereby opening new perspectives for clinical diagnosis.

1. Introduction

Social behavior and communication are largely determined by the efficient use and interpretation of nonverbal cues (Argyle, 1972), such as facial expressions. Emotional face processing has often been studied in individuals with autism spectrum disorder (ASD), a neurodevelopmental disorder characterized by impaired reciprocal social communication and interaction, including deficient non-verbal communicative behavior (American Psychiatric Association, 2014).

1.1 Facial emotion processing strategies in ASD

An abundance of behavioral studies has investigated emotion recognition in individuals with and without ASD, yielding mixed results in terms of group differences (Harms et al., 2010; Lozier et al., 2014; Uljarevic & Hamilton, 2013). Deficits in fear recognition, for instance, have often been shown in adults with ASD (Humphreys et al., 2007; Pelphrey et al., 2002; Rump et al., 2009; Wallace et al., 2008), whereas child studies often reported intact fear processing in ASD (Evers et al., 2015; Lacroix et al., 2014; Law Smith et al., 2010; Tracy et al., 2011). Due to the ongoing development of fear recognition abilities during childhood, floor effects in both ASD and control children might conceal possible group differences until they emerge during adulthood.

The use of alternative, less automatic processing strategies in ASD (Harms, 2010) might affect expression recognition. Perceptual processing styles are commonly investigated using the face-inversion paradigm, as inversion of the face disrupts the typical holistic or configural face processing (Rossion, 2008; Tanaka & Simonyi, 2016). Reports of an absent face inversion effect in ASD (Behrmann et al., 2006; Gross, 2008; Rosset et al., 2008) suggest the use of an atypical, more local and feature-based (emotion) processing style. However, other studies reported better emotion recognition in upright versus inverted faces, both in ASD and TD participants (McMahon et al., 2016; Wallace, 2008), indicating that participants with ASD are capable of holistic or configural face processing.

Difficulties in emotion processing may also occur when one fails to inspect the most relevant facial cues (Ellison & Massaro, 1997). The eyes have been suggested to play a crucial role in fear recognition (Bombari et al., 2013; Wegrzyn et al., 2017), but also the importance of the mouth, and the combination of both these regions, has been emphasized (Beaudry et al., 2014; Eisenbarth & Alpers, 2011; Gagnon et al., 2014; Guarnera et al., 2015). Results on the most informative facial features for emotion processing in ASD versus TD are inconclusive. Some studies demonstrated reliance on different facial cues for emotion recognition (Grossman & Tager-Flusberg, 2008; Neumann et al., 2006; Spezio et al., 2007), whereas other studies showed that both groups employ the same facial information (Leung et al., 2013; McMahon, 2016; Sawyer et al., 2012). Still, a similar way of looking at faces for reading emotions does not automatically imply similar neural processing, nor a similar level of emotion recognition performance (Sawyer, 2012).

1.2 Event Related Potential studies

To understand the neural basis of facial emotion processing in ASD, many researchers have measured Event-Related Potentials (ERPs) using electroencephalography (EEG) (Jeste & Nelson, 2009; Luckhardt et al., 2014), but generally fail to draw consistent conclusions (Black et al., 2017; Monteiro et al., 2017).

One ERP component of particular interest for (expressive) face processing is the N170 (Hinojosa et al., 2015). Kang and colleagues (2018) proposed this ERP component as a possible neural biomarker of the face processing impairments in individuals with ASD. However, the differences in N170 found between ASD and TD groups could merely reflect a slower general processing of social stimuli (Vettori et al., 2018) or they could be caused by carryover effects from changes in the immediately preceding P100 component (Hileman et al., 2011). In addition, atypicalities in the N170 response to emotional faces may not be autism-specific: similar atypicalities have been observed in other psychiatric and neurological disorders and may rather be an indication of emotional face processing dysfunction as a symptom of these diagnoses, than disorder-specific deficits (Feuerriegel et al., 2015).

The use of visual mismatch negativity (vMMN) paradigms has also been suggested as a clinically relevant application (Kremláček et al., 2016). However, the low number of oddballs and the low signal-to-noise ratio (SNR) of classic ERP measurements require many trials, resulting in long EEG recordings. Furthermore, to be valuable and reliable as a clinical tool, measurements should be consistent across studies and participants, in order to facilitate individual assessment. Yet, the variable expression of the vMMN in terms of individual timing and format (Kremláček, 2016) hampers the objective marking of the vMMN, especially at an individual level.

1.3 Fast periodic visual stimulation EEG

To overcome these difficulties, we used a relatively novel approach in the emotion-processing field, combining fast periodic visual stimulation (FPVS) with EEG. FPVS-EEG is based on the principle that brain activity synchronizes to a periodically flickering stimulus (Adrian & Matthews, 1934). Similar to previous studies (Dzhelyova et al., 2016; Leleu et al., 2018), we applied this principle in an oddball paradigm, where we periodically embedded expressive faces in a stream of neutral faces. The periodic presentation at predefined, yet different, base and oddball frequency rates makes FPVS-EEG a highly objective measure that supports direct quantification of the responses. Furthermore, the rapid presentation enables a fast acquisition of many discrimination responses in a short amount of time, with a high SNR. In addition, FPVS-EEG allows the collection of discriminative responses not only at a group level, but also at an individual level. Individual assessments may help us gain more insight in the heterogeneity within the autism spectrum.

1.4 Present study design

We applied FPVS-EEG in boys with and without ASD to quantify and understand the nature of the facial emotion processing difficulties in autism. We implemented fear as the deviant expression between series of neutral faces, because of its potential to elicit large neurophysiological responses (Nuske, Vivanti, & Dissanayake, 2014; Smith, 2012). By using neutral faces as forward and backward masks for the fearful faces in a rapidly presented stream (i.e. images are only presented for about 167 ms), the facial emotion processing system is put under tight temporal constraints (Alonso-Prieto et al., 2013; Dzhelyova, 2016). This allows us to selectively isolate the sensitivity to the expression.

Based on the literature, we expect a lower neural sensitivity (i.e. reduced EEG responses) for fearful expressions in children with ASD as compared to TD. Detection (i.e. the ability to notice that an emotional content is displayed in a facial expression) of fearful faces can occur without emotion categorization (i.e. the appraisal of which specific expression is shown) (Frank et al., 2018; Sweeny et al., 2013). Therefore, where possible group differences in emotion categorization might be concealed because of floor effects in both groups due to the ongoing development of fear recognition abilities, we expect that FPVS-EEG will reveal possible group differences in the implicit detection of rapidly presented fearful faces. In addition, series of upright as well as inverted faces are presented to assess possible differences in perceptual strategies. Here, we expect to observe more pronounced inversion effects in TD as compared to ASD children. Finally, we investigate whether the detection of a fearful face is modulated by directing the participants' attention to the eyes versus the mouth of the target face, by placing the fixation cross either on the nasion (i.e. nose bridge) or on the mouth of the face stimuli. This should inform us about the most informative facial cue for fear detection, and whether this most informative cue differs for children with ASD versus TD.

2. Methods

2.1 Participants

We recruited 46 8-to-12 year old boys without intellectual disability (FSIQ ≥ 70), comprising 23 TD boys and 23 boys with ASD. Given the higher prevalence of ASD in males (Haney, 2016; Loomes et al., 2017) and to avoid confounds due to gender effects on facial emotion processing (McClure, 2000), we only included boys in this study. In addition, given the "own-culture advantage" of emotion processing (Elfenbein & Ambady, 2002; Gendron et al., 2014), participants had to be living in Belgium for at least 5 years.

Children with ASD were recruited via the Autism Expertise Centre at the university hospital and via special need schools. TD participants were recruited via mainstream elementary schools and sport clubs. Four out of the 46 children were left-handed (2 TD), and three children reported colour blindness (1 TD). Because this did not affect their ability to detect the colour changes of the fixation cross, these participants were not excluded. All participants had normal or corrected-to-normal visual acuity. Five participants with ASD had a comorbid diagnosis of ADHD and seven participants of this group took medication to reduce symptoms related to ASD and/or ADHD (methylphenidate, aripiprazole).

Exclusion criteria were the suspicion or presence of a psychiatric, neurological, learning or developmental disorder (other than ASD or comorbid ADHD in ASD participants) in the participant or in a first-degree relative. To be included in the ASD group, the children needed a formal diagnosis of ASD, established by a multidisciplinary team, according to DSM-IV-TR or DSM-5 criteria (American Psychiatric Association, 2000; 2014). Furthermore, the Dutch parent version of the Social Responsiveness Scale (SRS; Roeyers et al., 2012) was used to measure ASD traits in all participants. A total *T*-score of 60 was employed as cut-off for inclusion, with all ASD children scoring above 60 and all TD children scoring below 60 to exclude the presence of substantial ASD symptoms.

Both participant groups were group-wise matched on chronological age and IQ. Participant demographics and descriptive statistics are displayed in Table 1.

The Medical Ethical Committee of the university hospital approved this study. Written informed consent according to the Declaration of Helsinki was gathered from the participants and their parents prior to participation.

TABLE 1. Characteristics of the participant groups

Measures	ASD group (*N* = 23) Mean (SD)	TD group (*N* = 23) Mean (SD)	Statistical comparison[a]	*p*
Age (years)	10.5 (1.4)	10.5 (1.4)	*t*(44) = .11	.91
Verbal IQ[b]	107 (11)	112 (11)	*t*(44) = -1.44	.16
Performance IQ[b]	104 (15)	108 (10)	*t*(44) = -1.16	.25
Full-scale IQ[b]	106 (9)	110 (9)	*t*(44) = -1.68	.10
Social Responsiveness Scale Total (*T* score)	85 (12)	42 (6)	*z* = 3.39	.000***
Social communication and interaction (*T* score)	83 (12)	41 (7)	*z* = 3.39	.000***
Restricted interests and repetitive behaviour (*T* score)	85 (11)	45 (4)	*z* = 3.39	.000***

Note. [a]*Statistical analyses by means of two-sample t test or Kolmogorov-Smirnov Z test (based on assumptions of normality and equal variances).* [b]*Intelligence was assessed using an abbreviated version (Sattler, 2001) of the Wechsler Intelligence Scale for Children, third edition (WISC-III-NL; Wechsler, 1992) with subscales Picture Completion, Block Design, Similarities, and Vocabulary. Participants were identical to the sample included in the study of Vettori and colleagues (2018), with the exception of four boys with ASD and two TD boys. *** p < .001*

2.2 Stimuli

The stimuli comprised a subset of the stimuli used by Dzhelyova and colleagues (2016). Full front images of a neutral and a fearful expression of four individuals – two males, two females – were selected from the Karolinska Directed Emotional Faces database (AF01, AF15, AM01, AM06, (Lundqvist et al., 1998)). The colored images were set to a size of 210 pixels x 290 pixels, equalizing 4.04° x 5.04° of visual angle at 80 cm viewing distance, and were placed against a gray background (RGB = 128, 128, 128; alpha = 255). The facial stimuli varied randomly in size between 80% and 120% of the original size. Mean pixel luminance and contrast of the faces was equalized during stimulus presentation.

2.3 Design

The design was similar to recent studies with fast periodic oddball paradigms (Dzhelyova, 2016; Vettori et al., 2019). The experiment consisted of four conditions – based on the orientation of the faces (upright or inverted) and the position of the fixation cross (nasion or mouth) – all repeated four times, resulting in 16 sequences. At the beginning of each sequence, a blank screen appeared for a variable duration of 2-5 seconds, followed by two seconds of gradually fading in (0-100%) of the stimuli. The images were presented for 40 seconds, followed by two seconds of gradually fading out (100-0%). The order of the conditions was counterbalanced, with the sequences randomised within each condition.

Stimuli of neutral faces (e.g. individual A) were displayed at a base rate of 6 Hz, periodically interleaved with a fearful oddball stimulus of the same individual every fifth image (6 Hz/5 = 1.2 Hz oddball rate; based on previous research (Alonso-Prieto, 2013; Dzhelyova & Rossion, 2014a; Liu-Shuang et al., 2014)), generating the following sequence $A_{\text{neutral}}A_{\text{neutral}}A_{\text{neutral}}A_{\text{neutral}}\mathbf{A}_{\textbf{fearful}}A_{\text{neutral}}A_{\text{neutral}}A_{\text{neutral}}A_{\text{neutral}}\mathbf{A}_{\textbf{fearful}}$ (see Figure 1 and the Movie in Online Resource 1). A custom application software written in Java was used to present images through sinusoidal contrast modulation (0-100%) (see also Figure 1).

2.4 Procedure

Participants were seated in a dimly lit room in front of a LCD 24-in. computer screen, which was placed at eye level. To guarantee attentiveness of the participants, an orthogonal task was implemented. A fixation cross, presented either on the nasion of the face or on the mouth, briefly (300 ms) changed color from black to red 10 times within every sequence. The participants had to respond as soon and accurately as possible when noticing the color changes of the fixation cross.

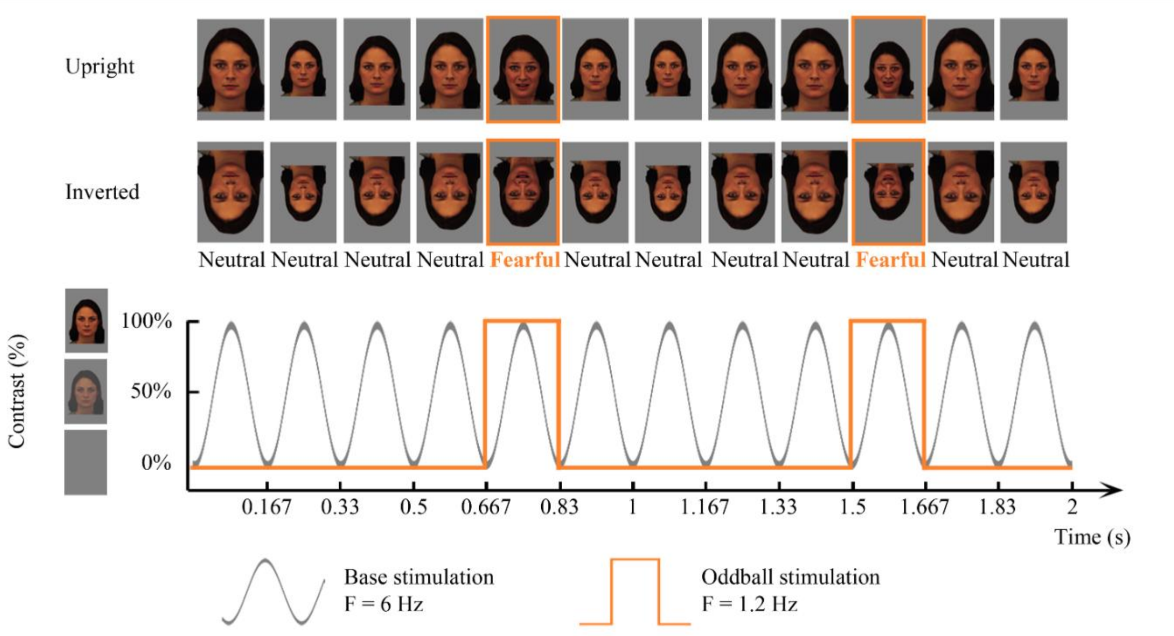

Figure 1. Fast periodic visual stimulation (FPVS) oddball paradigm for the detection of fearful faces, where neutral faces are presented sequentially at a fast 6 Hz base rate, periodically interleaved with a fearful face every fifth image (i.e. 1.2 Hz oddball rate). In separate trials, the faces are presented either upright or inverted and with the fixation cross on the nasion or on the mouth. (Dzhelyova, 2016).

2.4.1 EEG acquisition

We recorded EEG activity using a BIOSEMI Active-Two amplifier system with 64 Ag/AgCl electrodes and two additional electrodes as reference and ground electrodes (Common Mode Sense active electrode and Driven Right Leg passive electrode). We recorded vertical eye movements by positioning one electrode above and one below the right eye; additionally, one electrode was placed at the corner of both eyes to record horizontal eye movements. We recorded EEG and electrooculogram at 512 Hz.

2.4.2 EEG analysis

Preprocessing. We processed all EEG data using Letswave 6 (http://www.nocions.org/letswave/) in Matlab R2017b (The Mathworks, Inc.). We cropped the continuously recorded EEG data into segments of 45 seconds (2 s before and 3 s after each sequence), bandpass filtered it at 0.1-100 Hz using a fourth-order Butterworth filter, and resampled the data to 256 Hz. We applied independent component analysis via the runica algorithm (Bell & Sejnowski, 1995; Makeig et al., 1995) to remove blink artefacts for two TD participants who blinked on average more than 2SD above the mean (average number of blinks across participants = .19, SD = .22). We re-estimated noisy or artifact-ridden channels through linear interpolation of the three spatially nearest, neighboring electrodes. All data segments were re-referenced to a common average reference.

Frequency domain analysis. The preprocessed data segments were cropped to contain an integer number of 1.2 Hz cycles starting immediately after the fade-in until approximately 39.2 seconds (47 cycles). Data were then averaged in the time domain, for each participant individually and per condition. A fast fourier transformation (FFT) was applied to these averaged segments, yielding a spectrum ranging from 0 to 127.96 Hz with a spectral resolution of 0.025 (=1/40s).

The recorded EEG contains signals at frequencies that are integer multiples (harmonics) of the 6 Hz base stimulation frequency and the 1.2 Hz oddball frequency. To measure the discrimination response to fearful faces, only the amplitude at the frequencies corresponding to the oddball frequency and its harmonics (i.e. n*F/5 = 2.4 Hz, 3.6 Hz, 4.8 Hz, etc.) is considered (Dzhelyova, 2016). We used two measures to describe this fear discrimination response: SNR and baseline-corrected amplitudes. SNR is expressed as the amplitude value of a specific frequency bin divided by the average amplitude of the 20 surrounding frequency bins, whereas the baseline-corrected amplitude is calculated by subtracting the average amplitude level of the 20 surrounding bins from the amplitude of the frequency bin of interest (Liu-Shuang, 2014). We used SNR spectra for visualization, because the responses at high frequency ranges may be of small amplitude, but with a high SNR. Baseline-correction expresses responses in amplitudes (µV) that can be summed across significant harmonics to quantify an overall base and oddball response (Dzhelyova & Rossion, 2014b; Retter & Rossion, 2016).

To define the number of harmonics of the base and oddball frequencies to include in the analyses, for each condition we assessed the significance of the responses at different harmonics by calculating Z-scores (Liu-Shuang, 2014) on the FFT grand-averaged data across all electrodes and across electrodes in the relevant regions of interest (ROIs; cf. infra). We considered harmonics significant and relevant to include as long as the Z-score for two consecutive harmonics was above 1.64 ($p < .05$, one-tailed) across both groups and across all conditions (Retter, 2016). Following this principle, we quantified the oddball response as the sum of the responses of seven harmonics (i.e. 7F/5 = 8.4 Hz), without the harmonics corresponding to the base rate frequency (F = 6 Hz). The base frequency response was quantified as the summed responses of the base rate and its following two harmonics (2F and 3F = 12 Hz and 18 Hz, respectively).

In addition, analyses were performed at the individual subject level by calculating individual Z-scores for each of the relevant ROIs. We averaged the raw FFT spectrum per ROI and cropped it into segments centered at the oddball frequency and its harmonics, surrounded by 20 neighboring bins on each side that represent the noise level (Dzhelyova, 2016; Vettori, 2019). These spectra were summed across the significant harmonics and then transformed into a Z-score (see above).

Brain topographical analysis and determination of ROIs. Based on visual inspection of the topographical maps and in accordance with the identification of the left and right occipito-temporal region as most responsive for socially relevant oddball stimuli, and the medial occipital region as most responsive for base rate stimulation (Dzhelyova, 2016; Vettori, 2019), we defined the following ROIs: (1) left and right occipito-temporal (LOT and ROT) ROIs by averaging for each hemisphere the four channels with the highest summed baseline-corrected oddball response averaged across all conditions (i.e. channels P7, P9, PO7 and O1 for LOT, and P8, P10, PO8 and O2 for ROT), (2) medial occipital ROI (MO) by averaging the two channels with the largest common response at 6 Hz (i.e. channels Iz and Oz).

2.4.3 Behavioral facial expression measures

Two computerized behavioral facial expression processing tasks were administered.

The Emotion Recognition Task (Kessels et al., 2014; Montagne et al., 2007) investigates the explicit recognition of six dynamic basic facial expressions. Similar to the study of Evers and colleagues (2015), we applied two levels of emotion intensity: 50% and 100%. Children observe short video clips of a dynamic face in front view (4 clips per emotion), and have to select the corresponding emotion from the six written labels displayed left on the screen. Prior to task administration, participants were asked to provide an example situation for each emotion to ensure that they understood the emotion labels.

In the Emotion-matching task (Palermo et al., 2013) participants have to detect a target face showing a different facial emotion compared to two distractor faces both showing the same expression. The same six emotions as in the Emotion Recognition Task are involved. Here, we used the shorter 65-item version of the task, preceded by four practice trials (for specifics, see Palermo et al., 2013).

2.4.4 Statistical analysis

For the statistical group-level analyses of the baseline-corrected amplitudes, we applied a linear mixed-model ANOVA (function 'lmer' (package 'lme4') in R (Bates et al., 2015)), fitted with restricted maximum likelihood. Separate models were fitted with either the base or the oddball rate response as the dependent variable. Fixation (eyes vs. mouth), orientation (upright vs. inverted faces) and ROI (LOT, ROT, MO) were added as fixed within-subject factors, and group (ASD vs. TD) as a fixed between-subject factor. To account for the repeated testing, we included a random intercept per participant. Degrees of freedom were calculated using the Kenward-Roger method. Planned posthoc contrasts were tested for significance using a Bonferroni correction for multiple comparisons, by multiplying the p-values by the number of comparisons.

In addition to the group-level analyses, we also evaluated the significance of the fear detection response for each individual participant based on their z-scores. Responses were considered significant if the z-score in one of the three ROIs exceeded 1.64 (i.e. $p < .05$; one-tailed: signal > noise).

Subsequently, we applied a linear discriminant analysis (LDA) on the EEG data to classify individuals as either belonging to the ASD or TD group. We carried out a variable selection ('gamboost' function in R (Buehlmann et al., 2018)) to identify the most informative predictors, resulting in 12 input vectors for the LDA model – i.e. the first four oddball harmonics for each of the three ROIs. We expect them to be highly correlated, however, these between-predictor correlations are handled by the LDA (Kuhn & Johnson, 2013). Before performing the LDA classification, assumptions were checked. A Henze-Zirklers test ($\alpha = .05$) with supplementary Mardia's skewness and kurtosis measures showed a multivariate normal distribution of the variables. A Box's M-test ($\alpha = .05$) revealed equal covariance matrices for both groups. In addition, we assessed the competence of the classification model to address the issues of small sample sizes and possible over-fitting by carrying out permutation tests (Noirhomme et al., 2014).

For the behavioral data of the orthogonal task and the Emotion-matching task, the assumptions of normality and homoscedasticity were checked using a Shapiro-Wilk and Levene's test, respectively. For normal distributions, an independent-samples T-test was applied, otherwise, we performed a Mann-Whitney U test. When the assumption of homogeneity of variances was violated, degrees of freedom were corrected using the Welch-Sattertwaite method. For the Emotion Recognition Task, we applied a linear mixed-model ANOVA, with intensity level (50% vs. 100%) and expression (anger, fear, happiness, sadness, disgust, surprise) as fixed within-subject factors and group as between-subject factor. Again, we included a random intercept per participant.

All assumptions in terms of linearity, normality and constance of variance of residuals were verified and met for all linear mixed-model ANOVAs.

Due to equipment failure, data on the Emotion Recognition Task were missing for one TD participant. In addition, data of the Emotion-matching task were discarded for one TD participant because he did not follow the instructions and randomly pressed the buttons.

All analyses have been performed with and without inclusion of colorblind children, ASD children with comorbidities, and ASD children who take medication. As their inclusion/exclusion did not affect any results, we only report results with all participants included.

3. Results

3.1 General visual base rate responses

Clear brain responses were visible at the 6 Hz base rate and harmonics, reflecting the general visual response to the faces (Figure 2). The response was distributed over medial occipital sites. The linear mixed-model ANOVA revealed a highly significant main effect of ROI ($F(2,498) = 441.26$, $p = <.001$), with planned contrasts indicating highest responses in the MO region and lowest responses in the LOT region ($M_{LOT} = 2.49 < M_{ROT} = 3.19 < M_{MO} = 7.21$; $t(498)_{LOT\text{-}MO} = -27.52$, $t(498)_{LOT\text{-}ROT} = -4.07$, $t(498)_{ROT\text{-}MO} = -23.45$, all $p_{Bonferroni} < .001$).

There were no other significant main and/or interaction effects, suggesting similar synchronization to the flickering stimuli in the two participant groups (all *p* > .15).

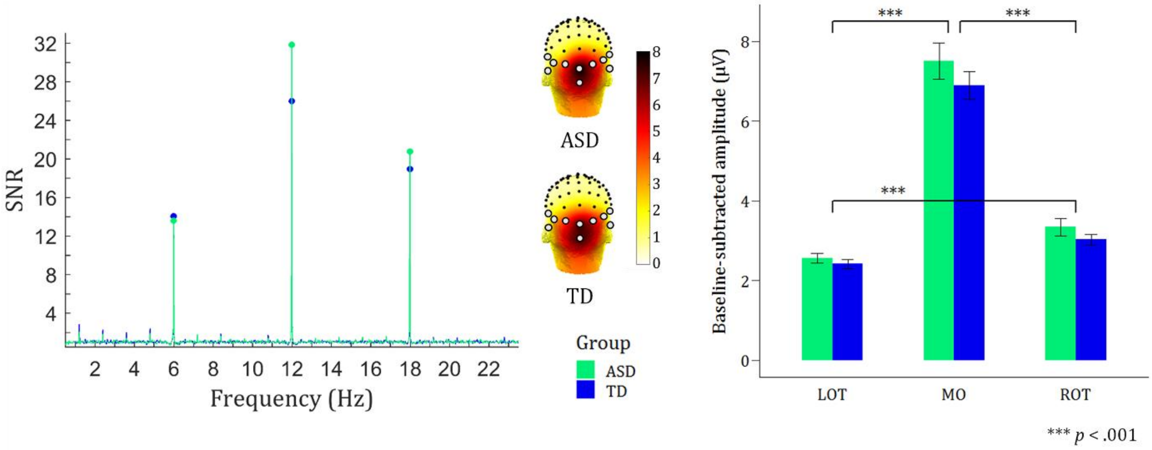

Figure 2. Similar general visual responses to faces in ASD and TDs. Left: SNR spectrum over the averaged electrodes of the MO region, with clear peaks at the base frequency (6 Hz) and its two subsequent harmonics (12 Hz and 18 Hz). Middle: Scalp distribution of the general visual base rate responses. The four most leftward and four most rightward open circles on the topographical map constitute LOT and ROT, respectively. The two central open circles constitute MO. Right: The summed baseline-subtracted amplitudes across the three harmonics of the base rate for each of the three ROIs (medial-occipital (MO) and left and right occipito-temporal (LOT and ROT) regions). Error bars indicate standard errors of the mean. The main effect of ROI is indicated on the bar graphs, with MO > LOT & ROT, and ROT > LOT.

3.2 Fear discrimination responses

Figure 3 visualizes clear fear discrimination responses in the four experimental conditions at the oddball frequency and its harmonics.

Most importantly, the linear mixed-model ANOVA of the fear detection responses showed a highly significant main effect of group, with higher responses in the TD group (M_{TD} = 1.69) versus the ASD group (M_{ASD} = 1.08, *F*(1,44) = 12.17, *p* = .001; Figure 4a). Additionally, the main effect for orientation of the presented faces (*F*(1,498) = 11.52, *p* < .001) indicated higher fear discrimination responses for upright versus inverted faces ($M_{inverted}$ = 1.28 < $M_{upright}$ = 1.49; Figure 4b). The main effect of fixation (*F*(1,498) = 155.51, *p* < .001) demonstrated much higher discrimination responses when the fixation cross is placed on the mouth versus the eyes (M_{eyes} = 1.01 < M_{mouth} = 1.76; Figure 4c). The absence of interactions with Group (all *p* > .56) indicated that all these effects were equally present in the TD and the ASD group. The linear mixed-model ANOVA yielded no main effect of ROI (*p* > .63).

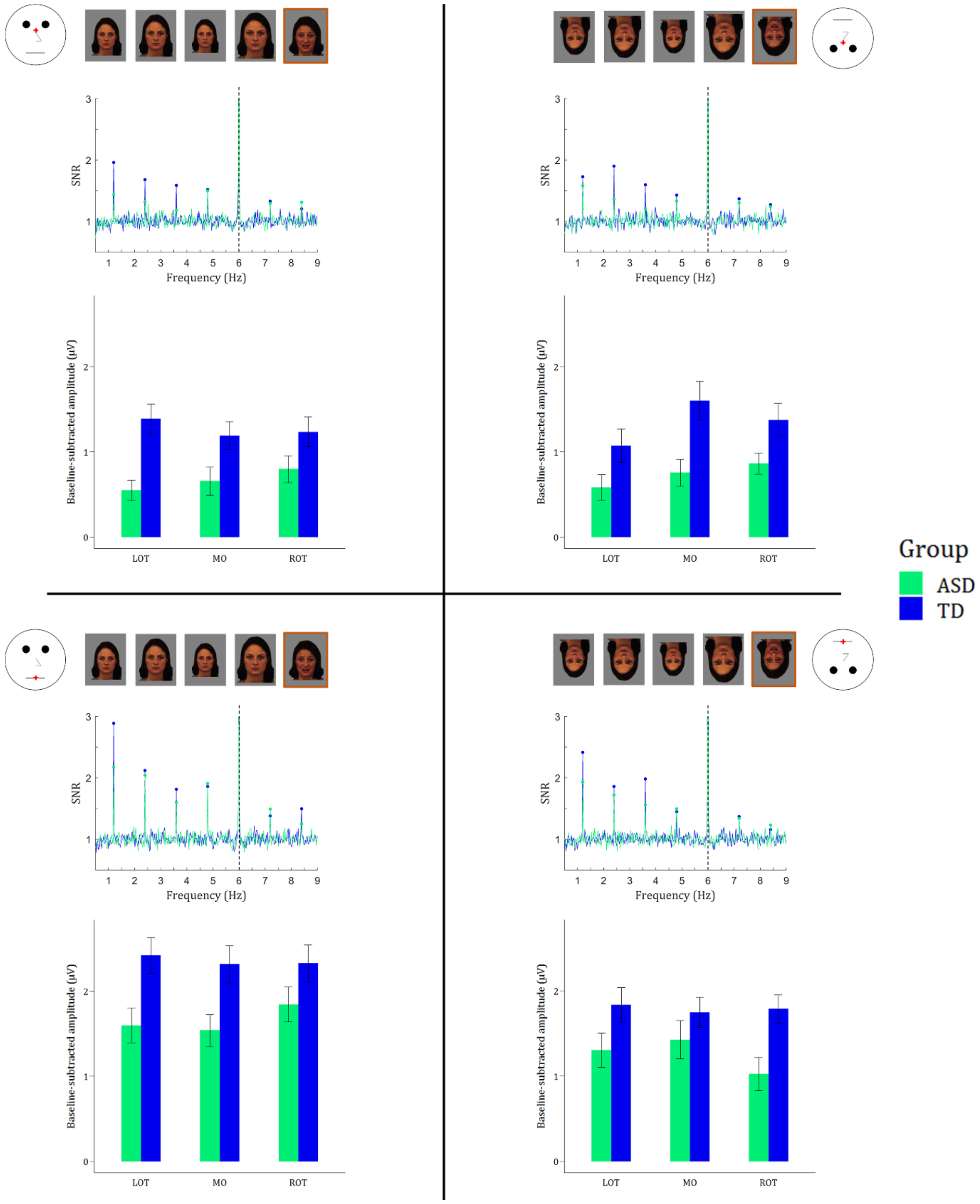

Figure 3. *Oddball responses for each experimental condition (based on the orientation of the face and the position of the fixation cross; eye fixation on the top, mouth fixation on the bottom) visualized via two measures: (1) SNR spectra averaged across the three ROIs, and (2) summed baseline-subtracted amplitudes for the seven first oddball harmonics (excluding 6 Hz; i.e. the dashed line) shown in bar graphs. Error bars reflect standard errors of the mean.*

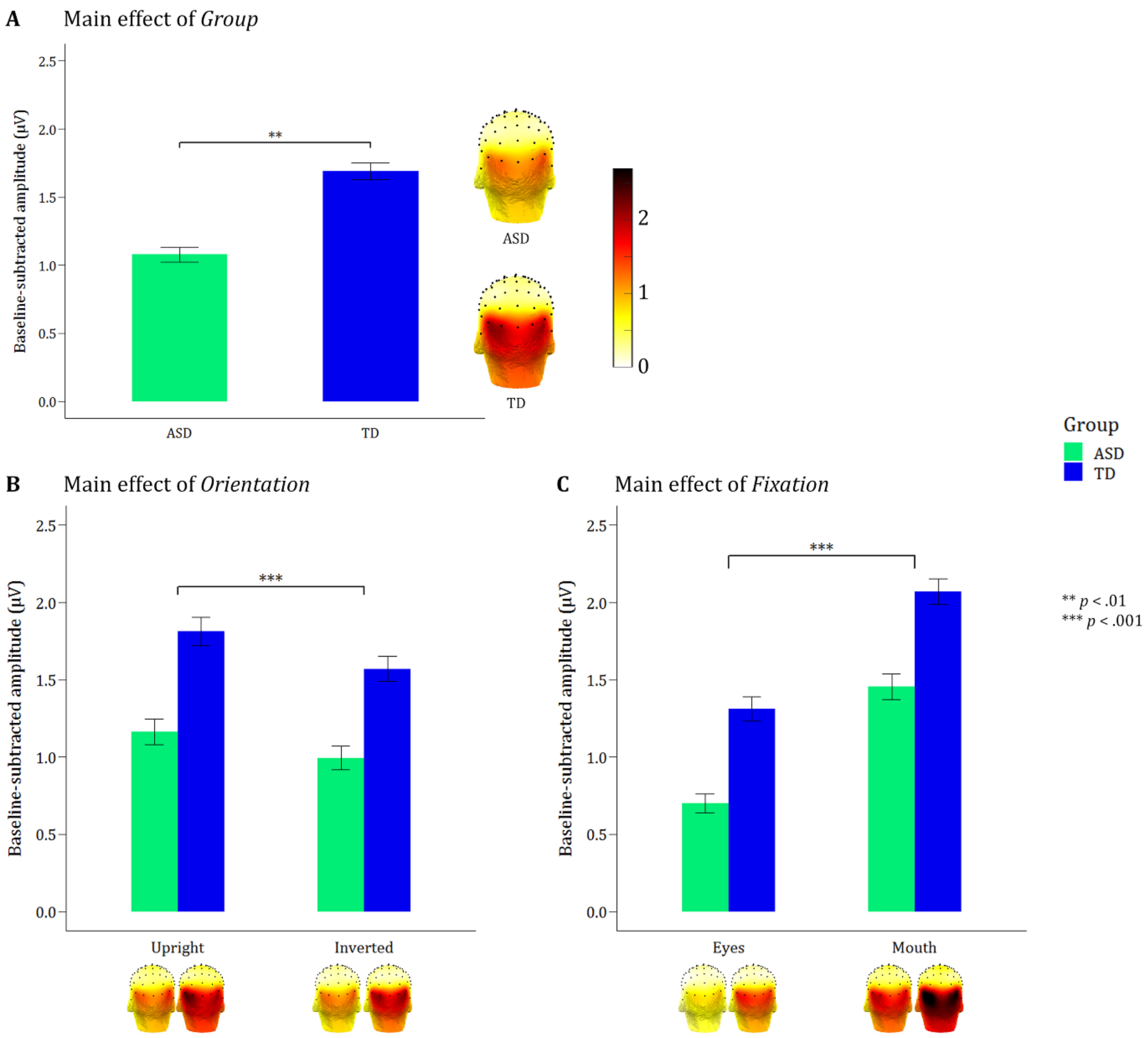

Figure 4. Main effects of Group, Orientation and Fixation. Mean fear discrimination responses (averaged across all three ROIs) of both participant groups in all experimental conditions, visualized via scalp topographies and bar graphs of the summed baseline-subtracted amplitudes for the included oddball harmonics (until 8.4 Hz, excluding the 6 Hz harmonic). Error bars are standard errors of the mean. ***(a)*** *The main effect of Group shows overall higher responses to fearful faces in the TD group compared to the ASD group. These significantly higher responses of the TD group remain visible in all conditions.* ***(b)*** *The main effect of Orientation demonstrates a clear inversion effect, with significantly higher fear discrimination responses to upright faces compared to inverted faces. (c) The main effect of Fixation reveals significantly higher responses when the fixation cross is placed on the mouth, compared to the eye region.*

Thus, the group analysis revealed large and significant quantitative differences in the amplitude of the fear discrimination response between TD and ASD. Yet, it is also important to investigate to what extent reliable fear discrimination responses can be recorded at the individual subject level. Statistical analysis of the individual subject data confirmed that all subjects but one boy with ASD (45/46) displayed a significant discrimination response for the most robust condition with upright faces and fixation cross on the mouth ($z > 1.64$, $p < .05$). See Table 2 for the results in all conditions.

TABLE 2. Number of individuals displaying significant individual fear discrimination responses

	ASD (*N* = 23)	TD (*N* = 23)
Upright + Mouth	22	23
Upright + Eyes	16	23
Inverted + Mouth	20	23
Inverted + Eyes	17	21

***Note**. Based on statistical analysis of the individual subject data. Fear discrimination responses were considered significant with z-scores > 1.64 (p < .05).*

Thus far, a reliable biomarker to distinguish people with and without ASD has not yet been established (Raznahan et al., 2009). To qualify as biomarker, objective quantifications of biological and functional processes are needed at the individual level (Mcpartland, 2016; McPartland, 2017), rather than mere statistical group differences. To evaluate the potential of our fear detection paradigm as a sensitive and objective marker of clinical status, we analyzed how well these responses can predict group membership of our participants. To understand how well the LDA classification generalizes, we relied on a leave-one-out cross-validation, which estimated an overall accuracy of 83% of the LDA model to predict group membership. More specifically, the sensitivity (i.e. correctly classifying individuals with ASD in the ASD group) and specificity (i.e. correctly classifying TD boys in the TD group) were estimated at 78% and 87%, respectively. The linear differentiation between both groups based on the full dataset is shown in Figure 5. Statistical assessment of the competence of the classification model demonstrated a likelihood of obtaining the observed accuracy by chance of p < .0001 for 10,000 permutations and additional inclusion of the neural responses of either the 7.2 Hz oddball harmonic or both the 7.2 Hz and 8.4 Hz oddball harmonics.

3.3 Behavioral measures: orthogonal task and explicit facial emotion processing

Results from the Mann-Whitney U test demonstrated equal accuracy (M_{ASD} = 90%, SD = 12; M_{TD} = 93%, SD = 6.8; W = 215, p = .54) and reaction times (M_{ASD} = 0.53 s, M_{TD} = 0.48 s, W = 296, p = .21) for both groups on the fixation cross color change detection task, suggesting a similar level of attention throughout the EEG experiment.

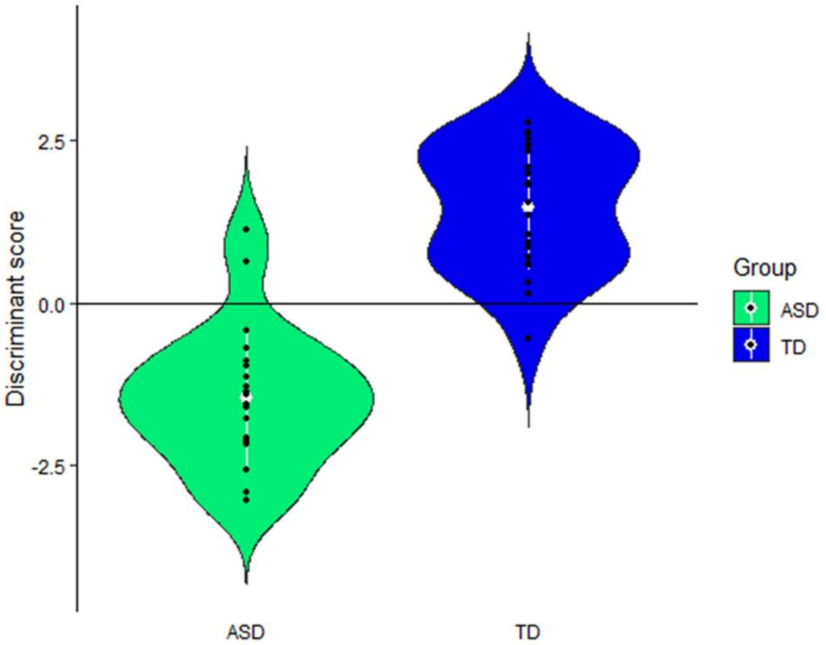

Figure 5. Violin plot of the LDA classification. The horizontal line represents the decision boundary of the LDA classifier and illustrates the differentiation between the two groups. When fitted to the full dataset, the LDA classifies 21 out of 23 participants with ASD and 22 out of 23 TD participants correctly. In white: mean +/- 1 SD.

For both explicit emotion processing computer tasks, all ASD and TD participants performed above chance level. A mixed-model ANOVA on the accuracy data of the Emotion Recognition Task showed that full-blown expressions were labelled more accurately compared to expressions presented at 50% intensity ($F(1,478) = 5.59$, $p = .019$). A main effect of emotion ($F(5,478) = 76.32$, $p < .001$) revealed that happy and angry faces were most often labelled correctly, whereas fearful and sad faces were the most difficult to label correctly. The main effect of group and the interaction effects were not significant (all $p >$ .40). To ensure that results were not driven by differential response biases, we calculated how often specific emotion labels were chosen by each individual. Since we did not find group differences in response bias (see appendix 1), there was no need to repeat the analysis with corrected performances.

Whereas both participant groups showed equal performance in terms of emotion labelling, a significant group difference was found for the matching of expressive faces, with the TD group outperforming the ASD group (M_{ASD} = 63%, SD = 11.0; M_{TD} = 69%, SD = 6.8; $t(37.01) = -2.29$, $p = .028$). No differences were found in reaction times (M_{ASD} = 4.27 s, M_{TD} = 4.24 s, $t(41.78) = 0.08$, $p = .94$).

4. Discussion

With FPVS-EEG, we evaluated the implicit neural sensitivity of school-aged boys with and without ASD to detect briefly presented fearful faces among a stream of neutral faces, and we investigated to what extent this sensitivity is influenced by the orientation of the face and by attentional focus to the eye versus mouth region. In addition, we analyzed the performance of both groups on two explicit tasks: an emotion labeling and an emotion matching task.

No group differences were found for the general visual base rate responses, indicating that the brains of children with and without ASD are equally capable of synchronizing with the periodically flickering stimuli, irrespective of the position of the fixation cross or the orientation of the presented faces. However, examination of the responses to changes in expression did reveal differences. We found an overall lower sensitivity to detect fearful faces in boys with ASD as compared to TD boys, regardless whether the faces were presented upright or inverted, or whether attention was oriented towards the eye or the mouth region. As there were no group differences in accuracy and response time of the performances on the orthogonal task, there is no evidence of less attention or motivation of the ASD participants. Analysis of the effects of the experimental conditions showed similar effects in both groups, with higher discrimination responses for upright versus inverted faces, and higher discrimination responses for fixations focused on the mouth versus the eyes. Results of the Emotion Recognition Task showed an equal performance in both groups, with a more accurate performance on the full blown versus half intensity expressions, and with more accurate labelling of happy and angry expressions as compared to sad and fearful expressions. Results on the Emotion-matching task did reveal a group difference, with the TD group outperforming the ASD group.

4.1 Neural responses children vs. adults

Clear responses to brief changes in facial expressions were visible in both participant groups, indicating that 8-to-12-year old boys can detect rapid changes to fearful expressions. Comparison of the brain responses of the TD boys in our sample with brain responses of healthy adults on an identical FPVS paradigm (Dzhelyova, 2016) reveals topographical differences for the oddball, but not for the base rate responses. Base rate responses of both children and adults were recorded over the medial occipital sites, spreading out bilaterally to the left and right occipito-temporal regions, with a right hemisphere advantage. The expression-change responses of adults were distributed over occipito-temporal sites, with a right hemisphere advantage (Dzhelyova, 2016), whereas the oddball responses of the children in our study did not show this clear lateralization. The relatively larger involvement of MO in fear detection in children as compared to adults may reflect a relatively larger involvement of the primary visual cortex, and thus low-level visual processing (Dzhelyova, 2016, 2014a; Liu-Shuang, 2014). Indeed, the neural system involved in (expressive) face processing progressively specializes throughout development (Cohen Kadosh & Johnson, 2007; Leppänen & Nelson, 2009), which is mirrored by a shift in neural activation from a broader medial distribution in childhood to a more focused (bi-)lateral or unilateral distribution in adulthood (de Haan, 2011; Dzhelyova et al., 2016; Taylor, Batty, & Itier, 2004).

The typical age-related improvement in facial emotion processing (Herba et al., 2006; Herba & Phillips, 2004; Luyster et al., 2017) seems to be absent (Gepner, 2001; Rump, 2009), or at least less pronounced (Trevisan & Birmingham, 2016) in individuals with ASD. For example, although results are mixed, different latencies and/or amplitudes for the N170 component in ASD, relative to TDs, have been reported from early childhood (Dawson et al., 2004), extending throughout adolescence (Batty et al., 2011; Wang et al., 2004). However, different results when matching participants on verbal or mental age instead of chronological age suggest a developmental delay in specialized facial expression processing in children with ASD (Batty, 2011; De Jong et al., 2008), but the neural mechanisms across the developmental trajectory of facial expression processing in ASD remain unclear (Leung, 2018). Therefore, from a developmental perspective, applying this paradigm in children, adolescents and adults with ASD could clarify the course of the atypical maturation in individuals with ASD.

4.2 Reduced neural sensitivity to fearful faces in ASD

In terms of topographical distribution of the selective neural response to fearful faces, there is no difference between the ASD and TD group, suggesting the use of a similar emotional face processing network. However, given the progressive development of emotional face processing capacities in childhood, potential group differences in topography may still appear in adolescence and adulthood.

Turning towards the size of the selective response to the fearful faces, we do observe clear group differences, with lower amplitudes in the ASD sample. Given that adults with ASD display impaired emotion detection (Frank et al., 2018), it is not surprising that a deficit in this ability is already present during childhood. Importantly, the reduced neural sensitivity for detecting fearful faces among a stream of neutral faces is not due to deficits in implicitly detecting oddball categories per se. Indeed, a parallel study on a related group of 8-to-12 year old boys with ASD versus TD matched controls (Vettori, 2019) does show intact generic face categorization responses in children with ASD, indicating an equal sensitivity to implicitly detect faces within a stream of non-social images. However, boys with ASD were clearly less sensitive to detect the more subtle socio-communicative cues signaling the appearance of a different facial identity (Vettori, 2019). In the present study, we only used fearful faces to investigate facial expression discrimination. Including other emotions as well could elucidate whether facial emotion detection deficits in individuals with ASD are specific for fear, or if results may generalize to other facial expressions.

Previous studies have shown that age (Lozier, 2014; Luyster et al., 2017) and intellectual ability (Hileman, 2011; Trevisan & Birmingham, 2016) might influence emotion processing performance. As our participant groups were closely matched on age and IQ, the observed group difference in neural sensitivity to fearful faces cannot be attributed to these factors. Likewise, neither can the group difference be driven by a reduced focus of attention in the ASD group, given the equal performances of both groups on the orthogonal task. Five participants with ASD had a comorbid ADHD diagnosis, which may influence attention and be associated with emotion recognition deficits (Tye et al., 2014). Yet, exclusion of these participants did not alter the findings in any way, indicating that the observed group difference in oddball responses is strong and not driven by comorbid ADHD.

Another factor that could explain the differences in fear detection is social functioning. Social functioning has been found to be related to emotional face processing on the neural level (Dawson, 2004; Yeung et al., 2014). As evaluating this factor was out of the scope of our study, we did not collect early personal data on the social behavior of our participants, other than the SRS, nor did we administer additional behavioral tasks that could have tapped more into the social skills. Yet, future studies could further explore if and how differences in social functioning affect emotion perception.

4.3 Inversion affects fear detection

Face processing, both in terms of identity and expressions, typically involves a holistic/configural approach (Rossion, 2013; Tanaka & Farah, 1993). Accordingly, performance is typically disrupted by inverting faces and thereby forcing the use of a less efficient and more feature-based approach, i.e. the face inversion effect (Rossion, 2008; Tanaka, 2016). Previous studies with similar FPVS-EEG paradigms have indeed demonstrated significantly reduced oddball responses for identity (Liu-Shuang, 2014; Vettori, 2019) and emotion (Dzhelyova, 2016) discrimination in TD children and adults, respectively, when faces are presented upside-down compared to upright. Moreover, the study of Vettori and colleagues (2019) showed a strong inversion effect for facial identity discrimination in TD boys and an absent inversion effect in boys with ASD. These findings were interpreted as evidence for holistic face perception in TD, and a more feature-based face processing strategy in ASD (Vettori, 2019). In the current study, we find a significant face inversion effect in both the TD and ASD sample, suggesting that both groups generally apply a holistic facial expression processing approach, additionally supported by an effective feature-based approach. There is evidence that facial expression processing – and in particular fear detection (Bombari, 2013) – is more strongly determined by the processing of specific salient facial features instead of the configural relationship between those features (Sweeny et al., 2013). In our study, for instance, the open mouth in the fearful faces might have facilitated fear detection, also in the inverted condition.

4.4 Directing attention to the mouth facilitates fear detection

Evidence regarding the role of the eyes versus the mouth in fear recognition is mixed (Beaudry, 2014; Eisenbarth, 2011; Guarnera, 2015). In a similar vein, even though reduced eye contact is one of the clinical criteria of ASD (American Psychiatric Association, 2014), the empirical evidence that individuals with ASD focus less on the eyes and more on the mouth is not unequivocal (Bal et al., 2010; Black, 2017; Guillon et al., 2014; Nuske, Vivanti, Hudry, et al., 2014). Here, we do find higher fear discrimination responses in boys with ASD when their attention is directed towards the mouth instead of the eyes, which suggests that the mouth region is more informative for them than the eye region. However, rather unexpectedly, this was also the case in the TD group. Apparently, for both groups of children, the mouth is a more salient cue to rapidly detect fearful faces than the eyes. It has indeed been suggested that the mouth is the most informative area for expression processing (Blais et al., 2012) and that, when presented opened, it might enhance early automatic attention (Langeslag et al., 2018). Especially the presence of teeth tends to augment neural responses to expressive faces (DaSilva et al., 2016). The occurring contrast of white teeth against a darker mouth opening and lips might draw the attention. Although the images in our study were presented at a very fast rate, these low-level changes of the fearful mouth might elicit larger responses.

4.5 Implicit vs. explicit emotion processing

The contradicting findings on the behavioral face processing tasks align with the generally mixed findings in previous behavioral research (Lacroix, 2014; Uljarevic, 2013). Contrary to the implicit FPVS-EEG paradigm, explicit tasks allow the use of various verbal, perceptual and cognitive compensatory strategies (Harms, 2010), possibly aiding individuals with ASD to compensate for their intrinsic emotion processing deficits (Frank, 2018). These compensatory mechanisms, as well as task characteristics, could account for the mixed findings on behavioral discrimination between ASD and TD individuals (Jemel et al., 2006; Lozier, 2014; Nuske et al., 2013; Uljarevic, 2013), indicating the limited sensitivity of (certain) behavioral measures to pinpoint the socio-communicative impairments of individuals with ASD (Harms, 2010).

The (small) group difference found on the matching task might relate to the more feature based approach used by the ASD children to process facial expressions. As the target faces are paired with maximally confusable distractor emotions, involving similar low-level features (Palermo, 2013), reliance on the separate facial features instead of the configuration of the facial expressions may hamper accurate emotion matching in the ASD group.

5. Future research

In addition to the behavioral emotion matching or labelling tasks, an additional explicit emotion detection task at the same rapid presentation rate might allow to compare the implicit and explicit emotion discrimination abilities more directly in these samples.

Our results support the sensitivity of the FPVS-EEG approach to rapidly detect and quantify even small responses at an individual level (Dzhelyova, 2016; Liu-Shuang, 2014; Liu-Shuang et al., 2016). Furthermore, the predefined expression change frequency allows a direct and objective measurement of the discrimination response, without the complexity of post-hoc subtraction of the responses (Campanella et al., 2002; Gayle et al., 2012; Stefanics et al., 2012). It also tackles the hurdle of subjectively defining various components and time windows as is done with the standard ERP approach (Kremláček, 2016). Another asset of the FVPS-EEG approach is the fast acquisition of profuse discrimination responses in a short amount of time, because of the rapid stimulus presentation and the high signal-to-noise ratio. Whereas many trials and long recordings are needed in typical ERP studies to obtain reliable responses, we only need four stimulation sequences of 40 seconds to reliably measure implicit neural discrimination. All these advantages make it a suitable approach for studying populations that are often difficult to include in research, such as infants and people with low-functioning ASD. Furthermore, the promising result of the LDA classification shows the potential of this technique (possibly by combining several paradigms) to serve as a biomarker for ASD. However, to fully understand the potential of FPVS-EEG as a biomarker for socio-communicative deficits, more research is needed in (clinical) samples with a different age and/or IQ.

6. Conclusions

Our results indicate that children with ASD are less sensitive to rapidly and implicitly detect fearful faces among a stream of neutral faces, possibly contributing to difficulties with emotion processing. Both children with and without ASD apply a combined holistic and feature-based processing style, and rely mostly on information from the mouth region to detect the fearful faces.

The advantages of FPVS-EEG with its implicit nature, the strength of the effects, and its straightforward application and analysis, pave the way to including populations that are often excluded from studies because of verbal or cognitive constraints.

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Chapter 3

Rapid neural categorization of angry and fearful faces is specifically impaired in boys with ASD

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Published in *Journal of Child Psychology and Psychiatry*
(2020) 61(9). DOI: doi.org/10.1111/jcpp.13201

Abstract

Difficulties with facial expression processing may be associated with the characteristic social impairments in individuals with autism spectrum disorder (ASD). Emotional face processing in ASD has been investigated in an abundance of behavioral and EEG studies, yielding, however, mixed and inconsistent results. We combined fast periodic visual stimulation (FPVS) with EEG to assess the neural sensitivity to implicitly detect briefly presented facial expressions among a stream of neutral faces, in 23 boys with ASD and 23 matched typically developing (TD) boys. Neutral faces with different identities were presented at 6 Hz, periodically interleaved with an expressive face (angry, fearful, happy, sad in separate sequences) every fifth image (i.e. 1.2 Hz oddball frequency). These distinguishable frequency-tags for neutral and expressive stimuli allowed direct and objective quantification of the expression-categorization responses, needing only four sequences of 60 seconds of recording per condition. Both groups show equal neural synchronization to the general face stimulation and similar neural responses to happy and sad faces. However, the ASD group displays significantly reduced responses to angry and fearful faces, compared to TD boys. At the individual subject level, these neural responses allow to predict membership of the ASD-group with an accuracy of 87%. Whereas TD participants show a significantly lower sensitivity to sad faces than to the other expressions, ASD participants show an equally low sensitivity to all the expressions. Our results indicate an emotion-specific processing deficit, instead of a general emotion-processing problem: boys with ASD are less sensitive than TD boys to rapidly and implicitly detect angry and fearful faces. The implicit, fast and straightforward nature of FPVS-EEG opens new perspectives for clinical diagnosis.

1. Introduction

1.1 Facial emotion processing in ASD

Quick and adequate facial emotion processing is important for successful everyday social interactions, which is a daily struggle for many individuals with autism spectrum disorder (ASD), who are characterized by impaired social communication and interaction, including deficits in non-verbal communicative behavior (American Psychiatric Association, 2014). As difficulties in recognizing others' emotions are thought to contribute (partially) to the social deficits typically encountered in ASD (Gaigg, 2012), facial emotion processing has been investigated in an abundance of studies using different research techniques. However, results from these studies do not allow drawing consistent conclusions.

The results of behavioral face processing studies are mixed in terms of group differences between children, adolescents and adults with ASD versus typically developing (TD) individuals (Lozier et al., 2014; Uljarevic & Hamilton, 2013), ranging from intact emotion processing in ASD groups (Lacroix et al., 2014; Tracy et al., 2011), over emotion-specific impairments for negative (Whitaker et al., 2017; Wingenbach et al., 2017) or positive (Griffiths et al., 2017; Law Smith et al., 2010) expressions, to a general emotion recognition deficit (Evers et al., 2015; Xavier et al., 2015). These highly variable results may reflect the phenotypic heterogeneity in ASD but may also result from the variability and limited sensitivity of (certain) behavioral measures (Harms et al., 2010).

Electroencephalography (EEG) studies investigating the neural underpinnings of facial emotion processing in ASD also report inconsistent results. Some studies describe similar neural patterns in children and adolescents with ASD compared to typically developing controls (O'Connor et al., 2005; Wong et al., 2008). Others, however, have reported distinct neural responses in ASD groups, with smaller amplitudes and/or longer latencies for different ERP components, such as P100 (Batty et al., 2011), N170 (Batty, 2011; Hileman et al., 2011; Tye et al., 2014) or P200 (Dawson et al., 2004). These neural group differences have been found for all six basic expressions, as well as for neutral faces (Black et al., 2017; Monteiro et al., 2017).

1.2 Fast periodic visual stimulation EEG

Recently, EEG has been combined with Fast Periodic Visual Stimulation (FPVS) to selectively capture implicit neural sensitivity to brief changes in facial expressions. FPVS-EEG relies on the principle that brain activity synchronizes to a periodically flickering stimulus (Adrian & Matthews, 1934), and elicits a brain response at exactly the same frequency (Norcia et al., 2015).

Similar to previous studies (Dzhelyova et al., 2017; Poncet et al., 2019), we applied this principle in a facial expression oddball paradigm, by periodically interleaving a rapidly presented stream of neutral faces with expressive faces. The periodic presentation at predefined frequency rates generates distinguishable frequency-tags for the base and oddball stimuli, allowing direct quantification of the brain responses (Liu-Shuang et al., 2014). This makes FPVS-EEG a highly objective measure. In addition, the rapid presentation enables a fast acquisition of many neural responses indexing expression discrimination in only a few minutes of recording. Furthermore, FPVS-EEG allows the collection of reliable discriminative responses not only at a group level, but also at an individual level, allowing more insight in the heterogeneity within the autism spectrum.

1.3 Present study

With the present study, we consolidate and extend the findings of a lower neural sensitivity in school-aged boys with ASD to rapidly detect fearful faces, as compared to matched TDs (Van der Donck et al., 2019). Here, by applying FPVS-EEG with several facial emotions, we can broaden our understanding of the underlying neural nature of facial expression processing in ASD: is this lower neural sensitivity emotion-specific (e.g. only for fear) or general (i.e. generalizable to multiple expressions)?

We included angry, fearful, sad and happy faces as oddball stimuli in rapidly presented streams of neutral faces. These neutral faces act as forward and backward masks for the expressive faces, allowing us to selectively isolate the sensitivity to the expressions by putting the emotional face processing system under tight temporal constraints (Dzhelyova, 2017), without the influences of mechanisms other than fast and automatic emotion extraction. Notwithstanding the inconsistencies in the ASD-literature, group differences have most frequently been reported for negative expressions (Lozier, 2014; Uljarevic, 2013). Accordingly, and in line with the lower fear discrimination responses (Van der Donck, 2019), we mainly expect to observe lower neural sensitivity in the ASD group for fearful, angry and sad faces.

Importantly, unlike our previous study (Van der Donck, 2019), we continuously changed the identity of the faces (i.e. every image). This impedes expression discrimination based on low-level visual features, demanding higher-level face processing. Therefore, we expect neural responses to be mostly visible over higher-level occipito-temporal regions.

2. Methods

2.1 Participants

Participants were identical to the sample included in Van der Donck et al. (2019): 23 boys with ASD and 23 TD boys without intellectual disability (full scale IQ (FSIQ) ≥ 70), group-wise matched on chronological age and IQ. Intelligence was assessed using an abbreviated version (Sattler, 2001) of the Wechsler Intelligence Scale for Children, third edition (WISC-III-NL; (Wechsler, 1992)) with subscales Picture Completion, Block Design, Similarities, and Vocabulary. Combining Picture completion with Block Design, and Similarities with Vocabulary gives reliable and valid estimates of performance IQ (PIQ) and verbal IQ (VIQ), respectively. Additional behavioural measures (Emotion Recognition Task (Montagne et al., 2007) and Emotion-matching task (Palermo et al., 2013)) showed intact emotion labelling in the ASD group, yet, an impairment when matching facial expressions (for a detailed description of the assessment and the results of these behavioural tasks, see Van der Donck et al., 2019). See Table 1 for participant demographics and descriptive statistics.

Children with ASD were recruited via the Autism Expertise Centre at the university hospital and special need schools. TD participants were recruited via mainstream elementary schools and sport clubs. Exclusion criteria were the suspicion or presence of a psychiatric, neurological, learning or developmental disorder (other than ASD or comorbid ADHD in ASD participants) in the participant or a first-degree relative, based on information provided by the parents or provided in the multidisciplinary report. Children in the ASD group had a formal ASD-diagnosis, established by a multidisciplinary team, according to

DSM-IV-TR or DSM-5 criteria (American Psychiatric Association, 2000, 2014), and scored above 60 (total *T*-score) on the Social Responsiveness Scale (SRS, parent version (Roeyers et al., 2012)). The SRS reliably measures quantitative ASD traits and comprises five subscales that capture Receptive, Cognitive, Expressive and Motivational facets of social behaviour, and Autistic Preoccupations (Cronbach's α = 0.97; test-retest reliability = 0.81) (Constantino, 2013; Constantino & Gruber, 2005). A higher score indicates more severe ASD symptoms. TD boys scored below 60 on the SRS to exclude the presence of substantial ASD symptoms.

Measures	ASD group (*N* = 23) Mean (SD)	TD group (*N* = 23) Mean (SD)	Statistical comparison[a]	*p*
Age (years)	10.5 (1.4)	10.5 (1.4)	*t*(44) = .11	.91
Verbal IQ[b]	107 (11)	112 (11)	*t*(44) = -1.44	.16
Performance IQ[b]	104 (15)	108 (10)	*t*(44) = -1.16	.25
Full-scale IQ[b]	106 (9)	110 (9)	*t*(44) = -1.68	.10
Social Responsiveness Scale T score Total	85.13 (11.7)	41.65 (6)	*z* = 3.39	.000***
Emotion Recognition Task (% correct)	55.9 (32)	56.8 (34)	*F*(1,43) = 0.11	.74
Emotion-matching task (% correct)	63.1 (11)	69.4 (6.8)	*t*(37) = -2.29	.028*

Table 1. *Characteristics of the participant groups. [a]Statistical analyses using two-sample t test or Kolmogorov-Smirnov Z test (based on assumptions of normality and equal variances) or linear mixed-model. [b]Assessed via an abbreviated version (Sattler, 2001) of the Wechsler Intelligence Scale for Children, third edition (WISC-III-NL; (Wechsler, 1992)), with subscales Picture Completion, Block Design, Similarities, and Vocabulary. * p < .05 *** p < .001*

Four children were left-handed (2 TD), and three children reported colour-blindness (1 TD). As this did not affect their neural responses nor their ability to detect the colour changes of the fixation cross, these participants were not excluded. All participants had normal or corrected-to-normal visual acuity. Among the participants with ASD, five had a comorbid diagnosis of ADHD and seven took medication (methylphenidate, aripiprazole).

The Medical Ethical Committee of the university hospital approved this study. Written informed consent according to the Declaration of Helsinki was obtained from the participants and their parents. Participants received a monetary compensation and a small present of their choice.

2.2 Stimuli

The stimuli comprised full front images of 14 individuals (seven males, seven females) from the Karolinska Directed Emotional Faces database (Lundqvist et al., 1998), all displaying neutral, fearful, happy, sad and angry expressions. The colored images were set to a size of 300x450 pixels, equalizing 2.54°x3.29° of visual angle at 80 cm viewing distance, and were placed against a gray background. Mean pixel luminance and contrast of the faces were equalized during stimulus presentation.

2.3 Design

The design was similar to previous studies (Dzhelyova, 2017; Poncet, 2019). Neutral faces from continuously changing identities (i.e. every image) were displayed through sinusoidal contrast modulation (0-100%) at a 6 Hz base rate, periodically interleaved with an expressive oddball stimulus every fifth image (6 Hz/5 = 1.2 Hz oddball rate). At the beginning of each sequence, a blank screen appeared for a variable duration of 2-5 seconds. After two seconds of gradually fading in (0-100%), the images were presented for 60 seconds, followed by two seconds of gradually fading out (100-0%). Each of the four conditions (i.e. emotional expressions) was presented in a separate sequence and repeated four times, resulting in 16 sequences – all presented in a randomised order (Figure 1). The facial stimuli varied randomly in size between 80% and 120% of the original size.

2.4 Procedure

We conducted this study as part of a larger study on face processing in boys with ASD. Participants were seated in a dimly lit room at 80 cm viewing distance of a LCD 24-in. computer screen, placed at eye level. An orthogonal task was implemented to guarantee attentiveness of the participants. A fixation cross, presented on the nasion of the face, briefly (300 ms) changed color from black to red 10 times within every sequence. The participants had to respond as soon and accurately as possible when noticing the color changes.

2.4.1 EEG acquisition

We recorded EEG activity using a BIOSEMI Active-Two amplifier system with 64 Ag/AgCl electrodes and two additional electrodes as reference and ground electrodes (Common Mode Sense active electrode and Driven Right Leg passive electrode). Vertical eye movements were recorded via one electrode above and one below the right eye. One electrode was placed at the corner of both eyes to record horizontal eye movements. We recorded EEG and electrooculogram at 512 Hz.

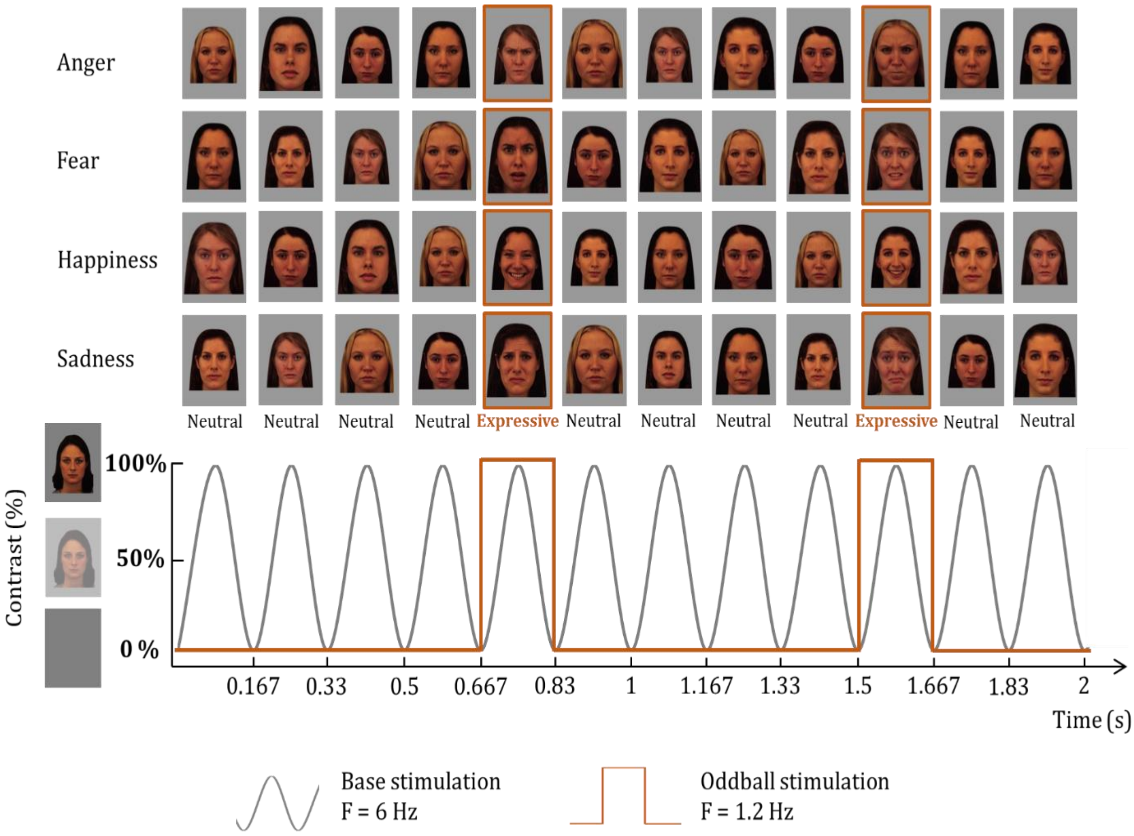

Figure 1. Fast periodic visual stimulation oddball paradigm: neutral faces are presented sequentially at a fast 6 Hz base rate, periodically interleaved with an expressive face – anger, fear, happiness, sadness – every fifth image (1.2 Hz oddball rate). The identity of the faces changes every image. Stimuli shown here: AF02, AF07, AF13, AF15, AF22, AF27, AF29 (Lundqvist et al., 1998)

2.4.2 EEG analysis

Preprocessing. We processed all EEG data using Letswave 6 (http://www.nocions.org/letswave/) in Matlab R2017b (The Mathworks, Inc.). We cropped the data into segments of 70 seconds (4 s before and 6 s after each sequence), applied a fourth-order Butterworth bandpass filter (0.1-100 Hz) and resampled the data to 256 Hz. For two participants (1 ASD, 1 TD) who blinked on average more than 2SD above the mean (average number of blinks per second across participants = .20, SD = .24), we applied independent component analysis via the runica algorithm (Makeig et al., 1995) and removed the component that accounted for most of the variance. We re-estimated noisy or artifact-ridden channels through linear interpolation of the three spatially nearest, neighboring electrodes; on average across all participants, one electrode was interpolated. All data segments were re-referenced to a common average reference.

Frequency domain analysis. The preprocessed data segments were cropped to contain an integer number of 1.2 Hz cycles starting immediately after the fade-in until approximately 59.2 seconds (71 cycles). After averaging the data in the time domain – per condition and for each participant individually – a fast fourier transformation (FFT) was applied, yielding a spectrum between 0 and 127.98 Hz with a spectral resolution of 0.017 (=1/60s).

The recorded EEG contains signals at frequencies that are integer multiples (harmonics) of the base and oddball frequencies. Only the amplitudes at the oddball frequency and its harmonics (i.e. n*F/5 = 2.4 Hz, 3.6 Hz, etc.) are considered as an index of facial expression discrimination (Dzhelyova, 2017). We used two measures for these responses: (a) signal-to-noise ratio (SNR), being the amplitude value of a specific frequency bin divided by the average amplitude of the 20 surrounding frequency bins (Rossion et al., 2012), and (b) baseline-corrected amplitudes, calculated by subtracting the average amplitude level of the 20 surrounding bins from the amplitude of the frequency bin of interest (Retter & Rossion, 2016). For both measures, these 20 surrounding bins are the 10 bins on each side of the target frequency bin, excluding the immediately neighboring bins and the two bins with the most extreme values. We used SNR spectra for visualization because responses at high frequency ranges may be of small amplitude, but with a high SNR. Baseline correction expresses responses in amplitudes (µV) that can be summed across significant harmonics to quantify the overall base and oddball response (Retter, 2016).

To define the number of base and oddball harmonics to include in the analyses, we assessed the significance of the responses at different harmonics by calculating Z-scores – using the mean and standard deviation of the 20 frequency bins surrounding the bin of interest (Liu-Shuang, 2014) – on the FFT grand-averaged data across all electrodes and across electrodes in the relevant regions of interest (ROIs; cf. infra). Harmonics were considered significant and relevant to include as long as the Z-score for two consecutive harmonics was above 1.64 ($p < .05$, one-tailed) across both groups and across all conditions (Retter, 2016). Following this principle, we quantified the oddball response as the sum of the responses of four harmonics (i.e. until 4F/5 = 4.8 Hz) and the base response as the summed responses of the base rate and its following two harmonics (2F and 3F = 12 Hz and 18 Hz, respectively).

In addition, analyses were performed at the individual subject level. We averaged the raw FFT spectrum per ROI and cropped it into segments centered at the oddball frequency and its harmonics, surrounded by 20 neighboring bins on each side that represent the noise level. These spectra were summed across the significant harmonics and transformed into an individual Z-score for each of the relevant ROIs.

Determination of ROIs. Visual inspection of the topographical maps and identification of the most responsive regions for emotional oddball and base rate stimulation (Dzhelyova, 2017) led to three ROIs. The left and right occipito-temporal (LOT and ROT) ROI were defined by averaging for each hemisphere the three channels with the highest summed baseline-corrected oddball response for each of the expressions (i.e. channels P7, P9 and PO7 for LOT, and P8, P10 and PO8 for ROT). The medial-occipital ROI (MO) was defined by averaging the two channels with the largest common response at 6 Hz (i.e. channels Iz and Oz).

2.5 Analyses

2.5.1 Quantification of physical stimulus characteristics

To assess to what extent neural discrimination responses are driven by low-level stimulus characteristics, we calculated the image-based difference between each of the emotional faces and each of the neutral faces in three manners. First, after aligning and cropping the faces to remove artefacts of hair and edges, a basic low-level image comparison was accomplished by computing the pixel-wise Euclidean distance (Op De Beeck et al., 2001) across the RGB-levels for each pair of neutral and expressive images per gender. Second, we created an average face per expression and gender, and again, calculated the Euclidean distance between the neutral and expressive faces. Third, to obtain a more higher-level image comparison, all face images were fed to a well-established facial expression recognition deep learning neural network, which was pre-trained on the FER2013 (Goodfellow et al., 2013) dataset consisting of around 36,000 labeled images (https://github.com/WuJie1010/Facial-Expression-Recognition.Pytorch). The output of the last fully connected layer of this network is a 512-dimensional vector representing the most discriminating features in the input image. Hence, the mean pairwise Euclidean distance between these low dimensional representations of neutral faces and each of the four expression categories was calculated.

2.5.2 Statistical analyses

For statistical group-level analyses of the baseline-corrected amplitudes in each ROI, we applied a linear mixed-model (function 'lmer' in R (Bates et al., 2015)), fitted with restricted maximum likelihood. Separate models were fitted with either the base or the oddball rate response as the dependent variable. *Expression* (anger, fear, happiness, sadness) and *ROI* (LOT, ROT, MO, and LOT, ROT for base and oddball responses, respectively) were added as fixed within-subject factors, and *Group* (ASD vs. TD) as a fixed between-subject factor. To account for the repeated testing, we included a random intercept per participant. Degrees of freedom were calculated using the Kenward-Roger method. Posthoc contrasts were tested for significance using a Bonferroni correction for multiple comparisons, by multiplying the p-values by the number of comparisons. All assumptions in terms of linearity, normality and constant variance of residuals were verified and met for all linear mixed-models.

MO base rate data points of one participant were discarded due to extreme outliers (amplitude > 15 µV). All analyses were performed with and without inclusion of colorblind children, ASD children with comorbidities, and ASD children on medication. As inclusion/exclusion did not influence the results, we report the analyses with all children included.

We also evaluated the significance of the expression-discrimination responses for all participants individually. Responses were considered significant if the z-score of the oddball frequency bin in the LOT or ROT region exceeded 1.64 (i.e. $p < .05$; one-tailed).

We performed a linear discriminant analysis (LDA) on the EEG data to classify participants as either belonging to the ASD or TD group. The input vectors comprised the most discriminative outcome measures, i.e. the response amplitudes to angry and fearful faces in the LOT and ROT regions. Assumptions of multivariate normal distribution and equal covariance matrices for both groups were checked and met. The competence of the classification model was assessed by means of permutation tests, which are robust for small sample sizes and possible over-fitting.

For performance on the fixation cross change detection task, assumptions of normality and homoscedasticity were checked using a Shapiro-Wilk and Levene's test, respectively. The assumption of homogeneous variances was met. Due to non-normal distribution of the data, we applied a Mann-Whitney U test. Due to equipment failure, data on this task is missing for two TD participants.

3. Results

3.1 Characterization of the stimulus properties

For each of the four emotional expressions, the (average) difference with the neutral facial expressions is depicted in Figure S1. Results of the raw pixel data show that the Euclidian distance towards the neutral faces is largely similar for all expressions (Figure S1a). However, the two higher-level measures (average faces (Figure S1b) and the deep learning neural network face differentiation (Figure S1c)) reveal that especially the happy faces are the most distinctive from the neutral faces.

3.2 Fixation cross change detection task

Results suggest a similar level of attention to the screen throughout the experiment for both groups, with equal accuracies (M_{ASD} = 90%, SD = 12; M_{TD} = 95%, SD = 5; W = 209, p = .46) and response times (M_{ASD} = .057 s, M_{TD} = 0.54 s; W = 271, p = .50) on this orthogonal task.

3.3 General visual base rate responses

Robust brain responses were visible at 6 Hz base rate and harmonics, mostly distributed over medial-occipital sites. Figure 2 shows the highly significant main effect of *ROI* (F(2,481) = 547.49, p <.001), with highest responses in the MO region and lowest responses in the LOT region ($t(481)_{LOT\text{-}MO} = -30.98$, $t(480)_{LOT\text{-}ROT} = -5.26$, $t(481)_{ROT\text{-}MO} = -25.76$, all $p_{Bonferroni} < .001$). The absence of any other significant main and/or interaction effect indicates a similar synchronization to the flickering stimuli in both groups (all p > .17).

3.4 Expression discrimination responses

All four expressions elicited clear expression-discrimination responses at the oddball frequency and its harmonics (Figure 3), clearly distributed over lateral occipito-temporal sites.

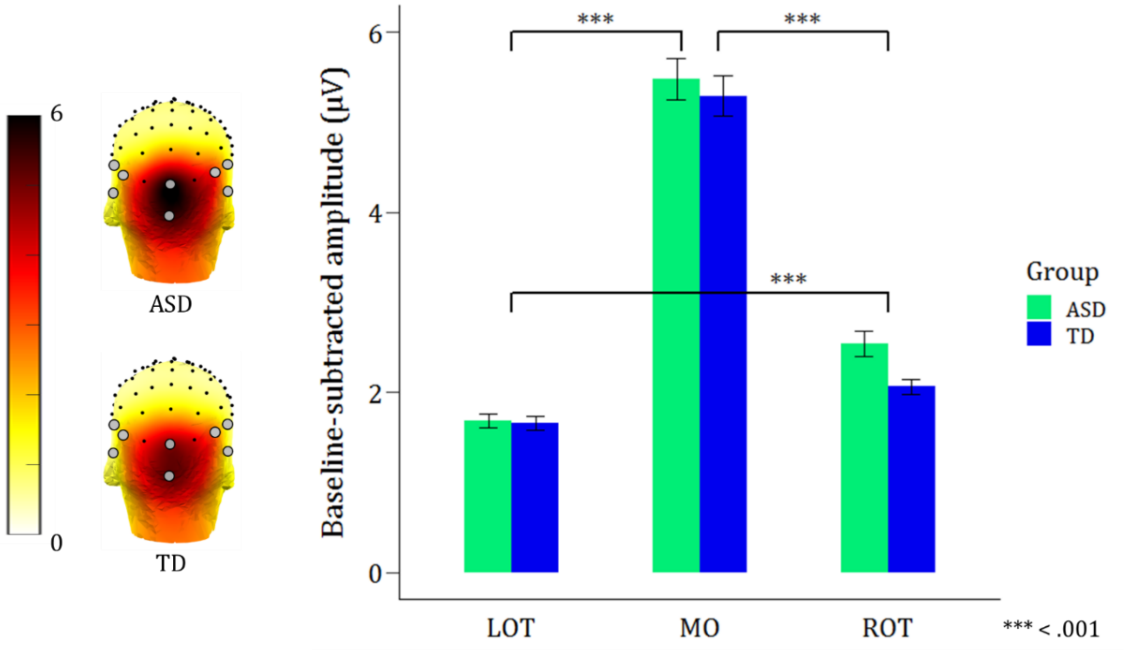

Figure 2. Similar general visual responses to faces in ASD and TD. ***Left:*** *Scalp distribution of the base rate responses. The three most leftward and three most rightward open circles constitute left and right occipito-temporal (LOT and ROT) regions, respectively. The two central open circles constitute the medial-occipital region (MO).* ***Right:*** *Summed baseline-subtracted amplitudes across the three harmonics of the base rate for each of the three ROIs, displaying a main effect of ROI. Error bars indicate standard errors of the mean.*

Statistical analysis of the expression-discrimination responses revealed main effects of *Group* (F(1,44) = 9.66, p = .003) and *Expression* (F(3,308) = 10.29, p < .001), which were further qualified by a significant interaction between *Group* and *Expression* (F(3,308) = 4.58, p = .004). Only angry ($t(190)_{\text{ASD-TD}} = -3.86$, $p_{Bonferroni} = .003$) and fearful ($t(190)_{\text{ASD-TD}} = -3.29$, $p_{Bonferroni} < .05$) faces elicited significantly higher responses in the TD compared to the ASD group. No group differences were found for happy and sad faces (all $p_{Bonferroni} > .98$). Furthermore, the effect of expression only applied to the TD group, with significantly lower responses to sad faces, compared to the three other expressions ($t(308)_{\text{anger-sad}} = 6.15$, $p_{Bonferroni} < .001$; $t(308)_{\text{fear-sad}} = 4.01$, $p_{Bonferroni} = .001$; $t(308)_{\text{happy-sad}} = 3.34$, $p_{Bonferroni} < .05$). In addition, the main effect of *ROI* (F(1,308) = 17.54, p < .001) revealed significantly higher responses in ROT compared to LOT region. See Figure 4 for all significant effects.

Although not the scope of this study, an additional analysis to specifically check for a threat-bias showed significantly higher responses to threatening (anger and fear) versus non-threatening (happiness and sadness) stimuli (F(1,316) = 10.25, p =.002), but only in the TD group (F(1,316) = 11.68, p < .001; $t(316)_{\text{threat-nonthreat}} = -4.68$, $p_{Bonferroni} < .0001$), not in the ASD group ($t(316)_{\text{threat-nonthreat}} = 0.153$, $p_{Bonferroni} > .05$).

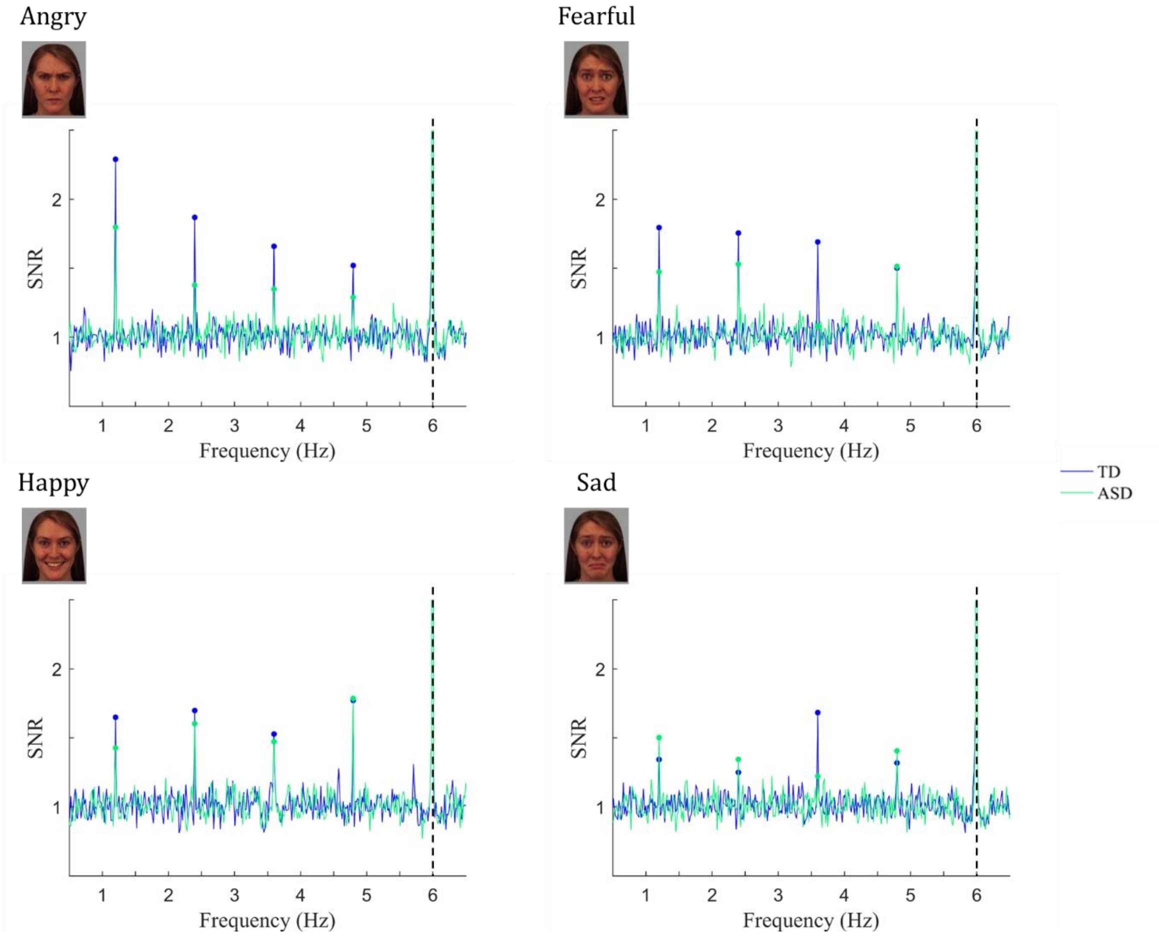

Figure 3. SNR-spectra visualizing the expression-discrimination responses, averaged over LOT and ROT regions, for each of the expressions and both groups. The significant first four harmonics are displayed; the dashed line indicates the 6 Hz base rate response.

Expression-discrimination responses at the individual subject level are displayed in Table S1, revealing that the majority of participants did show robust individual responses.

Despite the abundance of studies investigating biomarkers for ASD, a clinically applicable biomarker, reliable at the individual level, has not yet been developed (Mcpartland, 2016, 2017). We analyzed how well neural expression-discrimination responses for fearful and angry faces can predict group membership of our participants. By applying a leave-one-out cross validation, we assessed how well the LDA classification generalizes, revealing that 87% of the participants with ASD could be identified correctly. The overall accuracy of the

LDA model to predict group membership was estimated at 76%. Figure 5 shows the linear differentiation between both groups, based on the full dataset. The robustness of the classification model was statistically assessed by carrying out 10,000 permutations, demonstrating a likelihood of obtaining the observed accuracy by chance of *p* = .002.

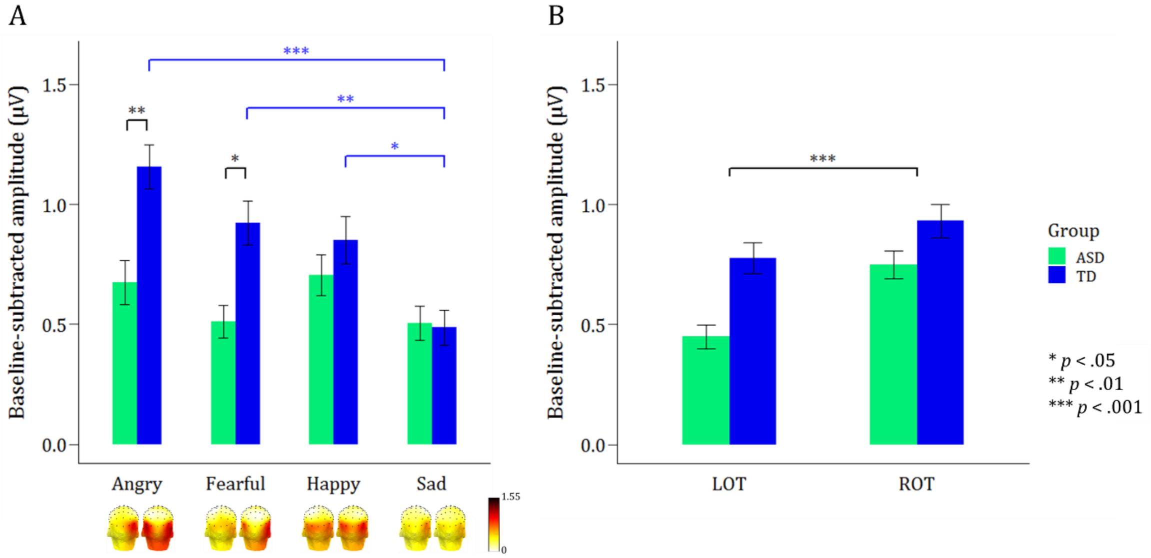

Figure 4. *Bar graphs of the summed baseline-subtracted amplitudes of both groups for the first four oddball harmonics (until 4.8 Hz) displaying mean expression-discrimination responses. Error bars reflect standard errors of the mean.* ***A.*** *Scalp topographies and bar graphs (averaged across LOT and ROT regions) displaying the mean responses per expression. The Group x Expression interaction shows significantly lower responses in the ASD versus TD group for angry and fearful faces (black asterisks), and an overall lower response to sad faces as compared to the other expressions in TDs (blue asterisks).* ***B.*** *The main effect of ROI revealed a right hemisphere advantage, with significantly higher responses in ROT versus LOT region.*

4. Discussion

Using FPVS-EEG, we assessed whether there is a difference in the neural sensitivity of school-aged boys with and without ASD to implicitly detect briefly presented facial expressions in a stream of neutral faces, and whether this differential sensitivity would be general (all expressions) or emotion-specific.

Our results indicate an equal neural synchronization to the general face stimulation and similar neural expression-discrimination responses for happy and sad faces, yet, a lower implicit sensitivity to angry and fearful faces in boys with ASD, as compared to TD boys. For the TD boys, fearful, angry and happy faces elicited stronger responses than sad faces. Given the equal performances of both groups on the orthogonal fixation cross task throughout all conditions, there is no evidence to attribute differences in neural responses across conditions or across groups to less motivation or attention of the participants.

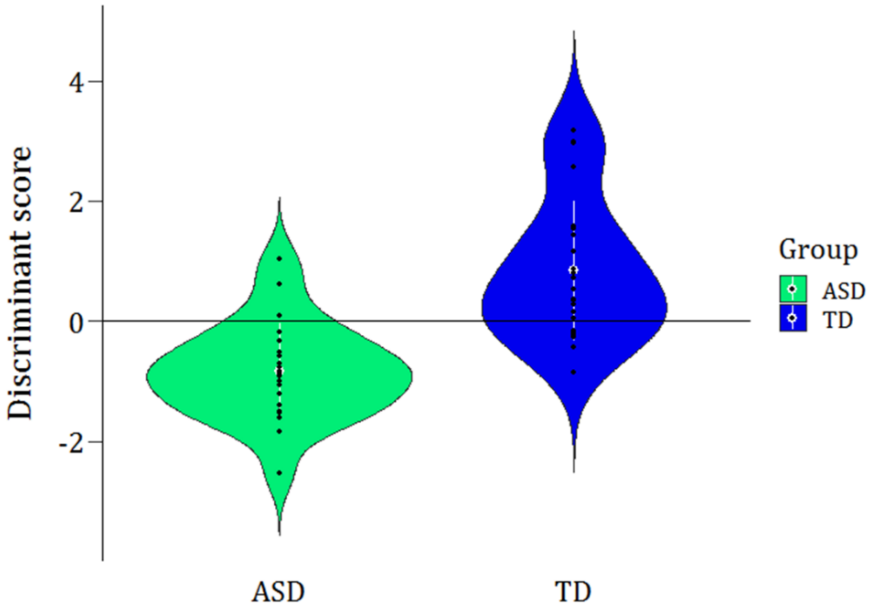

Figure 5. *Violin plot with the decision boundary of the LDA classifier (horizontal line) reflecting the differentiation between both participant groups. Based on the responses to facial anger and fear, the LDA classifies 20/23 participants with ASD and 17/23 TD participants correctly, when fitted to the full dataset. Mean +/- 1 SD is shown in white.*

4.1 Similar topographical maps in boys with and without ASD

The base and oddball stimuli elicited neural responses with similar topographical distributions in both groups. The base rate responses were mostly recorded over the middle occipital sites, suggesting the dominance of low-level visual processing (Norcia, 2015). In addition, both groups displayed more lateralized topographical activity patterns for the expression-discrimination responses, suggesting the use of a similar emotional face processing network in ASD and TD boys. However, considering the progressive development of typical facial expression processing capacities during childhood (Herba et al., 2006; Mancini et al., 2013), potential group differences in topography may still appear in adolescence or adulthood.

In our previous study investigating fear discrimination responses within a stream of faces with a single identity, the neural oddball responses were equally distributed across medial-occipital and occipito-temporal sites (Van der Donck, 2019). Here, however, the expression-discrimination responses are clearly distributed over occipito-temporal sites, with a right hemisphere advantage, and thereby resemble the topographical patterns of adults (Dzhelyova, 2017). These responses reflect the larger involvement of higher-level visual areas, probably induced by the continuously changing identities, which impedes low-level discriminatory processing to detect rapid changes in expression. Yet, even though also the boys with ASD were forced to mobilize a high-level processing approach with the current paradigm, this did not necessarily entail an equivalent high-level processing performance, as evidenced by the reduced neural sensitivity to changes in fearful and angry faces.

In adult populations, similar EEG paradigms elicited distinct topographical maps for different facial expressions (Dzhelyova, 2017; Poncet, 2019), suggesting the activation of (partially) distinct neural populations. Unlike these adult findings, the children's EEG responses did not show these separate spatial signatures for different expression changes. Again, this may point towards the ongoing developmental specialization and refinement of the neural systems involved in emotion processing (Leppänen & Nelson, 2009).

4.2 Reduced neural sensitivity to expressive faces in ASD is emotion-specific

We included four basic expressions (anger, fear, happiness, sadness) in our paradigm to assess the generalizability of the emotion processing impairment in ASD. Against a background of highly variable research findings (Black, 2017; Harms, 2010), we particularly expected a more pronounced impairment for discrimination of negative expressions.

The significant individual-subject discrimination responses in a large majority of participants across both groups indicate that boys with and without ASD can process facial affect fast and unintentionally, while attending faces without specifically focusing on the emotional expressions (Vuilleumier & Righart, 2011), allowing implicit detection of rapid emotion-changes. However, the response-amplitudes indicate a substantially reduced emotion-specific neural sensitivity in the ASD group: in contrast to studies describing a general emotion-processing deficit in ASD, we only observed selectively lower responses to angry and fearful faces, as compared to TDs. These findings confirm and extend our previously reported results (Van der Donck, 2019).

A threat-bias has often been reported in TD individuals, and has been related to evolutionary survival strategies (Hedger et al., 2016; Lyyra et al., 2014). The highest responses to anger and fear discrimination in the TD group do suggest a threat-detection advantage. The brain responses of the boys with ASD, however, do not point in that direction, despite reports of an anger-detection effect in ASD populations as well (May et al., 2016; Rosset et al., 2011). The threat-related content of the facial stimuli might selectively have boosted the oddball detection in the TD group only (Leung, 2019; Lyyra, 2014), resulting in the significant amplitude differences that allow a correct classification of 87% of the participants with ASD.

We found no group effect for the discrimination of sad faces. However, given the significantly lower detection responses in the TD group, possible floor effects may have masked potential group differences. Sadness has been found to be a difficult emotion to distinguish from neutrality (Gao & Maurer, 2010), possibly because it does not display very prominent, emotion-characteristic facial features (Calvo & Nummenmaa, 2008). This, combined with the complexity of continuously changing identities of the faces, might make it harder for children with and without ASD to detect the rapid changes to sadness in the blink of an eye.

Also happy faces elicited similar responses in both groups. Although recent reviews report differences in neural responses to happy faces (Black, 2017; Monteiro, 2017), happiness is recognized the earliest and easiest, needing only minimal signals (Whitaker, 2017). Intact detection of rapidly presented happy emotional faces in boys with ASD should therefore not be surprising.

4.3 The emotional content of the faces drives the neural responses

One might argue that the neural expression-discrimination responses simply reflect the low-level perceptual stimulus-based differences between base and oddball stimuli. Here, we present convincing evidence that these responses are determined by higher-level socio-affective processing abilities, at least in the TD participants. Indeed, if responses had been fully determined by stimulus properties, we would expect that the pattern of neural expression-discrimination responses would mirror the pattern of stimulus-based differences for each of these emotions relative to the neutral baseline. However, overall, the fine-grained evaluation of the stimulus properties demonstrated that this is not the case, because here the happy faces are singled out as the most distinctive. Accordingly, pertaining to the oddball responses in the TD group, the pattern of the neural amplitudes for the facial expressions does not match the stimulus differences, as here the angry and fearful faces yielded the highest responses. This suggests that these amplitude differences are caused by higher-level socio-emotional relevance and saliency, possibly within the context of an evolutionary threat-superiority effect. In the ASD participants, however, the brain responses seem to be more in line with the intrinsic stimulus characteristics (yet, without significant amplitude differences between the different emotions). Accordingly, contrary to the TD group, this might suggest a stronger reliance on the physical stimulus features instead of the emotional meaning of the stimulus. This observation resonates with previous accounts of atypical perceptual processing in ASD, such as the Enhanced Perceptual Functioning (Mottron et al., 2006) and the Weak Central Coherence (Happé & Frith, 2006) account, which propose that perceptual processing in ASD is more feature-based and locally oriented, whereas in TD it is more globally driven and oriented towards integrating information into a meaningful whole (gestalt).

4.4 Limitations and future research

In the present study, we only included four basic expressions. As children will be confronted with a wider range of facial emotions in daily life, adding also surprise and disgust, and maybe even more complex or more subtle expressions, to the paradigm may increase the ecological validity and give us a broader understanding of the abilities of individuals with ASD to automatically and rapidly process socio-affective details.

Since studies have revealed a female advantage for facial expression processing, also in children (McClure, 2000), it might be interesting to apply this paradigm in girls. Girls with ASD tend to be better at masking their social difficulties than boys with ASD (Hull et al., 2017), possibly concealing facial expression processing differences between girls with ASD and TD girls on an explicit behavioral level. However, neural differences to rapidly detect facial emotions might be uncovered with this implicit paradigm.

Our results confirm that FPVS-EEG is a highly sensitive and objective measure to detect and quantify even small responses at an individual level, in a short amount of time, thanks to the rapid, frequency-tagged stimulus presentation. Only four sequences of 60 seconds are required to obtain reliable implicit neural expression-discrimination responses. With all its advantages, FPVS-EEG is a well-suited technique to study populations that are otherwise difficult to include in research because of cognitive or verbal constraints. Furthermore, the promising classification results of the LDA demonstrate the potential of this approach to serve as a biomarker for socio-communicative deficits. However, more research in (clinical) samples with a different IQ and/or age is needed to understand the full potential of FPVS-EEG.

5. Conclusion

Our results indicate an emotion-specific processing deficit instead of a general emotion-processing problem in ASD. Boys with ASD are less sensitive to rapidly and implicitly detect angry and fearful faces among a stream of neutral faces. There is no evidence of a negative emotion processing deficit in ASD, as their discrimination responses to sad faces were similar to those of TD boys. However, the overall lower responses to sadness in the TD group, as compared to the other expressions, may have concealed possible group differences. Additionally, the responses elicited by happy faces were equal in both groups.

The implicit and straightforward nature of FPVS-EEG, as well as the strength of the effects, pave the way to include populations that are often excluded from research due to cognitive or verbal constraints.

6. Supplementary materials

	ASD (N = 23)	TD (N = 23)
Anger	18	22
Fear	18	21
Happiness	21	19
Sadness	17	15

***Table S1.** Number of individuals displaying significant emotion-discrimination responses for each of the conditions, based on statistical analysis of the individual subject data (i.e. z-scores > 1.64 (p < .05)).*

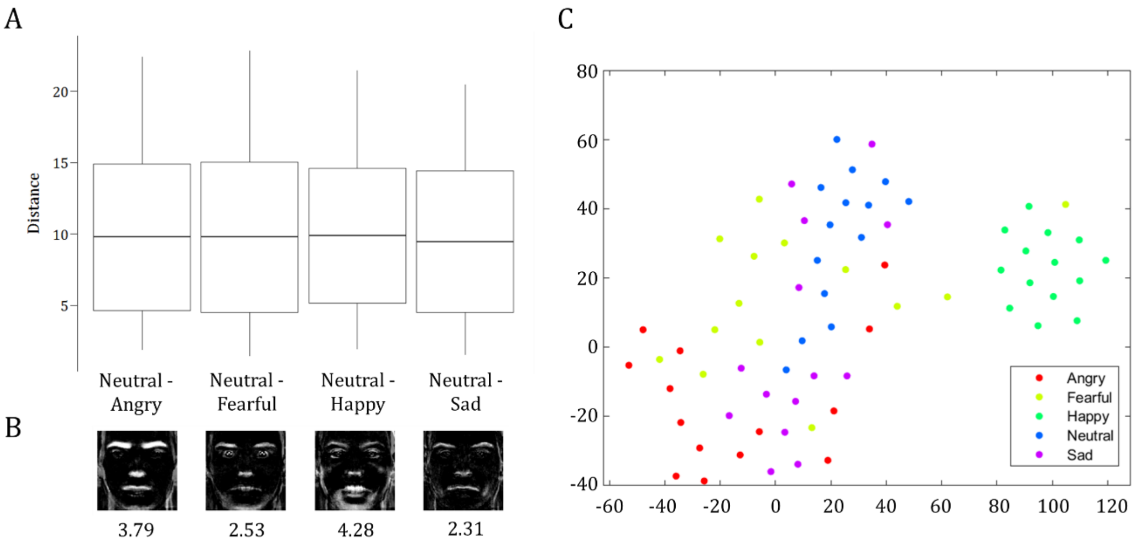

***Figure S1.** Physical characterization of the expressive versus neutral faces. **A.** Pixel-wise Euclidean distances (boxplots, based on mean +/- 1SD, whiskers reflect the minimum and maximum distance). **B.** Visualization and values of the mean Euclidean distance between the averaged neutral face and the average of each of the expressive faces. Lighter shadings indicate the face parts that are the most different from the neutral face. C. 2D visualization of the embedding space for all the face images (14 identities per expression), obtained from their 512-dimensional representations in the facial expression recognition deep learning neural network according to t-SNE algorithm* (van der Maaten & Hinton, 2008). *Mean Euclidean distances between neutral and sad, fearful, angry, or happy faces in this latent space equal 3.25, 4.31, 5.63, and 7.50, respectively.*

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Chapter 4

Investigating automatic emotion processing in boys with ASD via eye tracking and facial mimicry recordings

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Submitted to *Autism Research*.

Abstract

Difficulties in automatic emotion processing in individuals with autism spectrum disorder (ASD) might remain concealed in behavioral studies due to the use of compensatory strategies. To gain more insight in the mechanisms underlying facial emotion recognition, we recorded eye tracking and facial mimicry data of 20 school-aged boys with ASD and 20 matched typically developing (TD) controls while performing an explicit emotion recognition task. Looking times to specific face regions (eyes, nose and mouth) were analyzed and face exploration dynamics were modeled by mapping temporal scan paths using observable Markov models. Facial mimicry was assessed using automatic video decoding via FaceReader computer vision software. Boys with ASD and TDs were equally capable to recognize and label expressions and did not differ in proportional looking times, and number and duration of fixations. Yet, specific facial expressions elicited particular gaze patterns within the TD group. Both groups showed similar face scanning dynamics, although boys with ASD demonstrated smaller saccadic amplitudes. Regarding the facial mimicry, we found no emotion specific facial responses and no group differences in the responses to the displayed facial expressions. Our results indicate that boys with and without ASD employ similar eye gaze strategies to recognize facial expressions. The smaller saccadic amplitudes in boys with ASD might indicate a less exploratory face processing strategy. Yet, this slightly more persistent visual scanning behavior in boys with ASD does not imply less efficient emotion information processing, given the equal behavioral performance. Results on the facial mimicry data indicate similar facial responses to emotional faces in boys with and without ASD.

1. Introduction

(Successful) social interactions are a daily struggle for many individuals with autism spectrum disorder (ASD) (American Psychiatric Association, 2014). These social deficits are thought to be strongly associated with difficulties in face processing, especially the processing of facial emotional expressions (Trevisan & Birmingham, 2016).

Facial emotion processing in individuals with and without ASD has been investigated in many behavioral studies, yielding, however, mixed and inconsistent results (Harms et al., 2010; Uljarevic & Hamilton, 2013), ranging from intact emotion processing in individuals with ASD (Lacroix et al., 2014; Tracy et al., 2011), over emotion-specific impairments for positive (Griffiths et al., 2017; Law Smith et al., 2010) or negative (Whitaker et al., 2017; Wingenbach et al., 2017) facial expressions, to a general emotion recognition deficit (Evers et al., 2015; Xavier et al., 2015). These highly variable results might reflect the large phenotypic heterogeneity but may also result from the large variability and limited sensitivity of (certain) behavioral measures (Harms, 2010). In addition, the interpretation of explicit emotion processing results can be impeded due to mechanisms beyond facial expression processing per se.

1.1 Eye gaze behavior

To overcome influences of compensatory strategies (Rutherford & McIntosh, 2007) and to gain more insight in the underlying mechanisms of (emotional) face processing in ASD, researchers have turned to measures tapping more automatic social processing behavior, such as visual processing strategies. Indeed, eye tracking studies have sought to elucidate the characteristic mechanisms of facial expression processing deficits in individuals with ASD. As facial expressions are produced by activating particular face muscles (Ekman & Friesen, 1978), adequate face scanning patterns are required to identify different emotions. Research has shown that typically developing (TD) individuals tend to vary their scanning patterns in relation to the emotional content of the face (Beaudry et al., 2014), with, for example, more fixations on the eyes or mouth when being presented with negative or positive emotions, respectively (Eisenbarth & Alpers, 2011; Wegrzyn et al., 2017). Individuals with ASD, on the other hand, show less of this differentiation (Åsberg Johnels et al., 2017). However, as with much of the emotion processing literature in ASD, results are mixed (Black et al., 2017; Papagiannopoulou et al., 2014). For example, similar eye gaze patterns during emotional face processing have been reported, with equal gaze to the eyes of positive and negative expressions in both groups (Falck-ytter et al., 2010; Leung et al., 2013). Yet, both groups have also been found to recognize facial expressions better when relying on information from the mouth (McMahon et al., 2016). Other results have indicated divergent face scanning: both implicit and explicit tasks have revealed a preferential looking towards the mouth instead of the eyes in children with ASD, as compared to TD children (Bal et al., 2010; Nuske et al., 2014), or a tendency to look more outside the core facial features in both children (Nuske, 2014) and adults (Pelphrey et al., 2002) with ASD. In addition, researchers also observed differences in fixation duration, with shorter fixations in individuals with ASD when looking at fearful faces (Nuske, 2014) or rather longer fixations irrespective of facial expression (Leung, 2013). Overall, possible differences in gaze behavior strategies towards emotional faces might account for differences in facial expression recognition performance, as difficulties in emotion processing may occur when one fails to inspect the most relevant facial cues (Ellison & Massaro, 1997). On the other hand, a similar way of looking at faces to read emotions neither implies a similar level of emotion recognition performance (Sawyer et al., 2012).

1.2 Facial mimicry

Another measure tapping automatic and implicit social responsivity is facial mimicry. Spontaneous facial mimicry refers to the unintended, unconscious mirroring of others' emotional facial expressions that occurs automatically within the first few seconds after seeing one's expression (Mathersul et al., 2013; Moody et al., 2018). During social interactions, TD individuals have the natural tendency to mirror the expressions of their interaction partner (Duffy & Chartrand, 2015; Lakin, 2013; Sonnby-Borgström, 2016), as it facilitates affiliation (Kavanagh & Winkielman, 2016; Lakin & Chartrand, 2003), fosters affective and cognitive empathy towards each other (Drimalla et al., 2019) and boosts prosocial behavior (Stel et al., 2010; Van Baaren et al., 2004). However, certain situational contexts rather call for counter- or complementary mimicry (Beall et al., 2008; Seibt et al., 2015; Stel, 2010), demonstrating the importance of correctly assessing whom, when and how to mimic (Kavanagh, 2016).

This default tendency to automatically mimic the facial expressions of the interaction partner may lack in individuals with ASD (Moody & McIntosh, 2006; Trevisan et al., 2018; Vivanti & Hamilton, 2014). Although some studies using facial electromyography (EMG) or video analysis via the Facial Action Coding System (FACS; (Ekman, 1978)) reported intact (Deschamps et al., 2013; Schulte-Rüther et al., 2017) or even enhanced (Magnée et al., 2007) facial mimicry in ASD, the majority of studies found reduced or delayed facial mimicry to different facial expressions in adults (McIntosh et al., 2006; Yoshimura et al., 2015) and children (Beall, 2008; Oberman et al., 2009; Stel et al., 2008) with ASD, as compared to TD controls. Importantly, given the evidence of intact voluntary facial mimicry in ASD (McIntosh, 2006; Oberman, 2009; Stel, 2008), this deficit seems not due to more basic impairments in perception or praxis.

Subsequently, these impairments in spontaneous facial mimicry in ASD may impact on more complex socio-emotional processing (Moody, 2006; Trevisan, 2018), such as explicit emotion recognition (Weiss et al., 2019). Indeed, numerous studies have suggested that spontaneous facial mimicry is associated with emotion recognition performance (Borgomaneri et al., 2020; Lakin, 2013; Neal & Chartrand, 2011), indicating that mimicking a perceived expression might support its perceptual recognition (Hess & Fischer, 2014; McIntosh, 1996). As a result, in ASD, deficits in facial mimicry might contribute to difficulties with emotion recognition.

1.3 Present study

In previous studies, we observed an emotion-specific lower neural sensitivity for facial expression discrimination in boys with ASD versus TD controls, implicitly measured via frequency-tagging electroencephalography, in spite of equal emotion processing accuracy at the behavioral level (Van der Donck et al., 2020, 2019). Here, we wanted to broaden our understanding of possible underlying differences in facial emotion processing mechanisms by simultaneously investigating gaze behavior and spontaneous facial mimicry of 20 boys with ASD and 20 matched TD boys while performing an explicit facial expression labelling task.

More specifically, the present study aims to identify possible group differences in gaze behavior while scanning dynamic emotional faces in order to recognize the expression. In addition to determining eye gaze characteristics in terms of duration, saccadic amplitudes and number of fixations to specific facial features, we will also analyze the temporal scan paths using Markov models as a more comprehensive measure of the face exploration dynamics (Coutrot et al., 2018). Given the highly variable and contradicting results regarding eye gaze patterns during emotional face processing in ASD (Black, 2017), we did not have any strong expectations in terms of group differences. However, given the often reported greater attention to details (Vabalas & Freeth, 2016) and the feature-based perceptual face processing style in individuals with ASD (Behrmann et al., 2006; Gross, 2008; Rosset et al., 2008), we might expect to find longer fixations, as well as shorter saccadic amplitudes in boys with ASD versus TD boys, because of less frequent shifts between facial cues.

A more exploratory aim of this study was the investigation of facial mimicry presented by the participants while looking at the expressive faces. More specifically, we will explore whether boys with ASD differ in the extent and the temporal dynamics of their facial mimicry, in comparison to TD controls, by analyzing video recordings of the participants' concurrent facial expressions via FaceReader software (Noldus, 2016). Notwithstanding the inconsistencies in the ASD literature, group differences in facial mimicry have most frequently been reported (Beall, 2008; Oberman, 2009; Trevisan, 2018). Furthermore, a general reduction in facial expressivity has been included as one of the clinical characteristics of ASD (American Psychiatric Association, 2014). Accordingly, we expect to observe a generally reduced or delayed facial mimicry of boys with ASD, compared to TD boys, yet, acknowledging the results of a recent meta-analysis that did not provide evidence to support the claim of less intensely expressed facial emotions in individuals with ASD (Trevisan, 2018).

2. Method

2.1 Participants

Participants comprised a subsample of the sample included in Van der Donck et al. (2020, 2019), with the exception of one newly included TD boy. Twenty boys with ASD and 20 TD boys without intellectual disability (full-scale IQ ≥ 70), group-wise matched on chronological age and IQ, participated in the study. Intelligence was assessed using an abbreviated version (Sattler, 2001) of the Wechsler Intelligence Scale for Children, third edition (WISC-III-NL; Wechsler, 1992), by combining subscales Picture Completion and Block Design, and subscales Similarities and Vocabulary to get reliable and valid estimates of performance IQ and verbal IQ, respectively.

Three out of the 40 children were left-handed (1 TD) and all participants had normal or corrected-to-normal vision. Five participants with ASD had a comorbid diagnosis of ADHD and six participants of this group took medication to reduce symptoms related to ASD and/or ADHD (methylphenidate, aripiprazole). Although less common, a side-effect of aripiprazole is mask-like facial expressions (Chew et al., 2017) because of reduced movement and animation of the facial muscles. As this participant's facial mimicry results did not differ from the other participants with ASD and given the similar statistical results with this participant included versus excluded, this participant was not excluded from the reported analysis. All analyses were performed with and without inclusion of boys with ASD with comorbidities, and boys with ASD on medication. As inclusion/exclusion did not influence the results, we report the analyses with all children included

Children with ASD were recruited via the Autism Expertise Centre at the University Hospitals Leuven and via special need schools. TD participants were recruited via mainstream elementary schools and sport clubs. Exclusion criteria were the suspicion or presence of a psychiatric, neurological, learning or developmental disorder (other than ASD or comorbid ADHD in ASD participants) in the participant or a first-degree relative, based on information provided by the parents or provided in the multidisciplinary report. Children in the ASD group had a formal ASD-diagnosis, established by a multidisciplinary team, according to DSM-IV-TR or DSM-5 criteria (American Psychiatric Association, 2000, 2014), and scored above 60 (total *T*-score) on the Social Responsiveness Scale (SRS, parent version (Roeyers et al., 2012)). A higher score indicates more severe ASD symptoms. TD boys scored below 60 on the SRS to exclude the presence of substantial ASD symptoms. See Table 1 for participant demographics and descriptive statistics.

The Medical Ethical Committee of the university hospital approved this study. Written informed consent according to the Declaration of Helsinki was gathered from the participants and their parents prior to participation. Participants received a monetary compensation and a small present of their choice.

2.2 Stimuli

The stimuli were selected from the Emotion Recognition Task (Kessels et al., 2014; Montagne et al., 2007) and comprised computer-generated morphs of colored static emotional images of four individuals (2 males, 2 females), evolving dynamically from a neutral expression towards a full-blown emotional expression (see (Montagne, 2007) for details about the stimuli). The dynamic facial expressions included the six basic emotions: anger, fear, happiness, sadness, disgust and surprise. The duration of the video clips was approximately 1.5 seconds. The stimuli of 600 x 600 pixels subtended 9.93° of visual angle at 60 cm viewing distance.

Table 1. Characteristics of the participant groups

Measures	ASD group (*N* = 20) Mean (SD)	TD group (*N* = 20) Mean (SD)	Statistical comparison[a]	*p*
Age (years)	10.4 (1.4)	10.5 (1.3)	$t(38) = -0.31$	.76
Verbal IQ	107 (12)	111 (11)	$t(38) = -1.16$	.25
Performance IQ	104 (15)	109 (14)	$t(38) = -1.24$	.22
Full-scale IQ	106 (10)	111 (11)	$t(38) = -1.54$	.13
Social Responsiveness Scale				
Total (*T*-score)	86 (12)	42 (7)	W = 400	< .001
Social communication and interaction (*T*-score)	84 (13)	42 (7)	W = 400	< .001
Restricted interests and repetitive behavior (*T*-score)	86 (11)	45 (3)	W = 400	< .001

Note. [a]*Statistical analyses by means of two-sample t test or Mann-Whitney U test (based on assumptions of normality and equal variances).*

2.3 Procedure

We conducted this study as part of a larger study on facial expression processing in boys with ASD.

Participants were seated in a dimly lit room at 60 cm viewing distance of an LCD 24-in. computer screen, placed at eye level. Videos of the participants' faces, as well as their eye gazes were continuously recorded while performing the Emotion Recognition Task (Kessels, 2014; Montagne, 2007), which investigates the explicit recognition of six dynamic basic facial expressions. Children observed short video clips of a dynamic face in front view (4 clips per emotion), always starting from a neutral face towards the full-blown emotional expression, and had to select the corresponding emotion from the six written labels displayed left on the screen. The last frame of the video clip remained visible while the participants responded. Prior to task administration, participants were asked to provide an example situation for each emotion to ensure that they understood the emotion labels. The task lasted approximately seven minutes. All participants performed this task for the second time (see (Van der Donck, 2019)), yet, this time, only with the dynamic full-blown expressions.

2.4 Eye tracking

2.4.1 Eye tracking recording

Eye tracking data were collected using a Tobii X3-120 screen-based remote eye tracker – running at 120 Hz – and Tobii Pro software (Tobii Pro). For this eye tracking device, binocular gaze accuracy and precision at ideal conditions are estimated at 0.4° and 0.24°, respectively (Tobii AB, 2017). As the participants were not restrained by a chinrest, yet, were instructed to hold their back against the back of the chair throughout the experiment, they could move their head within the dimensions of the headbox. The precision and accuracy of the recorded data may therefore differ at an individual level from those marketed by the manufacturers (Niehorster et al., 2018), independent from the identical apparatus-specific accuracy and precision. The standard five-point calibration procedure of the Tobii X3-120 yields a merely qualitative index of calibration quality based on visual inspection. In order to obtain a subject-specific *quantitative* measure of eye tracking data quality, we implemented an additional calibration validation paradigm, preceding the data registration (Vettori et al., 2020). Here, participants had to fixate on the center of nine consecutive fixation crosses appearing at different locations on the screen. Calculation of the angle between the vectors to the displayed fixation cross versus the actual gaze point yields a quantitative index of error angle (mean and variance) and resulting accuracy. These values were used in the analysis to attribute gaze points more accurately to particular areas of interest (AOIs).

Due to technical failure, eye tracking data was not recorded for four participants (two boys with ASD, two TD boys).

2.4.2 Eye tracking analysis

Determining fixations and AOIs. In line with Vettori et al. (2020), eye tracking data were analyzed using a series of custom-built scripts in Matlab (The Mathworks; https://github.com/TimVanWesemael/Fuzzy-AOI-EyeTracking). As head movements may lower the data quality of the participants' eye tracking recordings, we applied the I2MC algorithm (identification by 2-means clustering (Hessels et al., 2017)) to filter the raw eye tracking data, which allows us to detect fixations across a wide range of noise and data loss levels in the recordings. The I2MC filter divides every gaze point in a specific time frame in two clusters, based on their proximity to the mean of each of the two clusters. Then, the number of chronological cluster membership transitions defines whether the gaze position signal contains a saccade (i.e. few membership transitions concentrated around a specific time point) or a fixation (i.e. frequent membership transitions across the whole time window). See Hessels et al. (2017) for a detailed description of the I2MC algorithm.

We defined our AOIs (eyes, mouth, nose) using the limited-radius Voronoi tessellation (LRVT), as it has been shown to be the most objective and noise-robust AOI defining method for facial stimuli (Hessels et al., 2016). The LRVT method uses a priori defined cell centers and a given radius to produce the AOIs. Because of our dynamic stimuli, we opted for a radius of 140 pixels to ensure that the AOIs comprised the same facial features in neutral versus expressive faces. In addition, to label all the fixation points that were not assigned to any of the AOIs, we defined the area 'outside AOI'.

Gaze attribution. Fixations are assigned to the AOIs depending on their closeness to the AOI cells' centers and the specified radius around those centers (Hessels, 2016), using probability weighting while taking into account the subject-specific data quality we obtained via the additional calibration validation procedure. More specifically, with this dimensional approach, a proportional score between zero and one is attributed to every AOI for every gaze point so that the cumulative sum of these scores equals one. These proportional scores indicate the probability that the corresponding AOI effectively contains the recorded gaze coordinate, and are based on a subject-specific two-dimensional bell curve around the gaze point with a standard deviation equal to the root-mean-square (RMS) registered during calibration validation (Van Wesemael, 2017). Hence, the calibration validation determines the probability weighting of the AOIs: better data quality results in more concentrated sample points around the gaze point, poorer data quality results in more dispersed sample points. Since the algorithm takes every gaze point into account, as well as the data quality, it proves to be a very reliable method (Vettori, 2020). For each AOI, the relative duration of all fixation points was averaged over the four video clips per facial emotion. Proportional looking times for each of the AOIs, as well as the proportion of looking time outside the AOIs, were calculated as a function of total time on the screen.

Face exploration dynamics. We modelled the temporal gaze behavior along the predefined face AOIs using first order Observable Markov Models (OMMs; i.e. based on observable events), via a custom Matlab implementation. The OMMs consist of a transition matrix, where elements represent the probabilities for the transitions of the fixation coordinates between the AOIs. The Markov property assumes this transition probability to be independent of the previous states. The model also requires the computation of the start probability for every AOI, which describes the probability of a sequence starting in that specific AOI (i.e. the first fixation point). Hence, for each participant, we constructed a single transition matrix, but we computed a separate start distribution for each initial presentation of a new face (i.e. for all 24 trials, based on the four video clips for each of the six basic expressions).

To fully characterize the face exploration dynamics, in addition to the OMM transition probabilities, we computed the number of fixations, the mean fixation duration, and the mean saccadic amplitude (i.e. measure of visual exploration (Vabalas, 2016)), by averaging the fixation durations and saccadic amplitudes extracted from the Tobii Pro output.

2.4.3 Statistical analysis

As most participants shifted their gaze to the labels presented on the left side of the screen shortly after stimulus presentation, we only included eye tracking recordings from the first two seconds after stimulus onset to analyze the participants' gaze and scan paths during actual facial expression recognition.

As a first rough measure of eye gaze behavior, we analyzed the **proportional looking time** for each of the AOIs using a linear mixed model (LMM; 'Afex' package in R (Singmann et al., 2020)) with *area of interest* (eyes, mouth, nose) and the *six basic expressions* as within-subject factors and *group* (ASD vs. TD) as between-subject factor. We included a random intercept and random slopes for AOI and facial expression per participant. Degrees of freedom were calculated using the Kenward–Roger method. Tukey-corrected post-hoc T-tests were performed on the fitted models using the 'emmeans' package (Lenth et al., 2020). Outlying data points were detected using the median absolute deviation and removed.

Although proportional looking time incorporates the number of fixations and their durations, we deemed it important to also take a closer look at these specific gaze characteristics to investigate the exploration paths. Therefore, we analyzed the number and the duration of the **fixations**, as well as the saccadic amplitudes. For the number and the duration of the fixations, we again applied a LMM, with the same within- and between-subject factors, random slopes and random intercept. The saccadic amplitudes were examined with an LMM across all AOIs and expressions.

Finally, we computed a MANOVA on the OMM transition matrix elements, as well as the three additional fixation measures, to investigate the statistical significance of possible group differences in **dynamic scanning patterns** of emotional faces. To do so, we constructed a 19-element property vector for each participant, containing all the dynamic gazing behavior features, i.e.: the 16 entries of the transition matrix, the mean number of fixations, the mean fixation duration and the mean saccadic amplitude. Given the short stimulus presentation duration and thus the small number of fixation transitions, we combined the data across all facial expressions to estimate the transition matrix. The 19 entries were standardized across all participants to a distribution with mean 0 and standard deviation of 1, to remove any dependency on the chosen scales, resulting in z-scores of the respective features. Finally, to account for the strong correlation among these 19 features, we performed a group-independent principal component analysis (PCA), based on Jolliffe's modification of Kaiser-Guttman (Cangelosi & Goriely, 2007; Jolliffe, 2002) to determine the number of components to retain. This PCA resulted in the retention of eight principal components, which were entered in the MANOVA. Based on the local outlier factor method, one participant from the ASD group was identified as outlier, and was consequently removed from the MANOVA group comparison analysis.

2.5 Facial mimicry

2.5.1 Facial expression recording

The camera used for the video recordings of the participants' faces (i.e. Microsoft Lifecam Studio with 1080p resolution) was positioned next to the computer screen, slightly below eye height.

2.5.2 Facial expression decoding

Analysis of the video recordings was carried out using FaceReader 7.1 (Noldus, 2016), set to analyze every frame (at a resolution of 24 frames per second). FaceReader 7.1 is trained to analyze the facial expressions produced by children (Noldus, 2016). After locating the face and creating an artificial face model based on over 500 key points, FaceReader calculates the deviation of the facial expression relative to a database of over 10,000 manually annotated emotional faces. Based on these calculations, FaceReader computes frame-by-frame intensity scores for the expression of each of the six basic emotions (ranging from 0 to 1) (Noldus, 2016; Uyl & Kuilenburg, 2005; see Kuilenburg, Wiering, & Uyl (2005) for a detailed description of the algorithm). Frequent failures to detect the face and decode the emotional expression (e.g. because of a hand in front of the participant's face) lead to a fragmentary output with missing data for several frames. To maintain data reliability, trials with less than 20% successful frames were excluded from the analyses. In addition, to minimize person-specific biases (e.g. naturally looking more happy or more angry), we calibrated each participant's facial expressions against that same individuals' neutral expression.

2.5.3 Statistical analysis

For each of the 24 trials, we extracted the timing and intensity of the peak expression intensity. Thus, for every single trial, we quantified at what time point and with what intensity each of the six basic emotions was present on the participant's face. Next, these time and intensity features were averaged across the four trials (i.e. identities) displaying an identical emotion. As we aimed at exploring spontaneous facial mimicry, we only included expressed emotions within a timeframe between 0.375 and 2 sec after stimulus onset, thus ranging from frame 9 (i.e. at 25% expression intensity) to frame 48 (i.e. half a second past reaching the full-blown 100% intensity expression).

As we were mainly interested in facial mimicry rather than overall facial responsivity, we performed a LMM investigating the **intensity** of the participant's expression, with *displayed emotion* (6 basic expressions) and *produced emotion* (6 basic expressions) as within-subject factors and *group* (ASD vs. TD) as between-subject factor, with a specific focus on the interaction between the displayed and produced expressions, and maybe even the three-way interaction including group. More specifically, if the participants would demonstrate facial mimicry, significantly higher intensities for the produced facial expression congruent to the displayed expressive face stimulus would be recorded, as compared to the other expressions. Next, if facial mimicry would be detected, an additional LMM with the same factors would be performed to assess potential group differences in the **timing** of the facial mimicry responses.

Degrees of freedom were calculated using the Kenward–Roger method and Tukey-corrected post-hoc T-tests were performed. Outlying data points were detected using the median absolute deviation and removed.

2.6 Behavioral facial expression recognition

We analyzed the participants' behavioral emotion labelling performances using a repeated measures ANOVA ('Afex' package (Singmann, 2020)). We examined the accuracy of the emotion recognition using the *six basic expressions* as within-subject factor and *group* (ASD vs. TD) as between-subject factor. Tukey-corrected post-hoc T-tests were performed on the fitted model for all significant effects ('emmeans' package (Lenth, 2020)). There were no outlying data points.

3. Results

3.1 Explicit facial expression recognition

All ASD and TD participants performed above chance level on the Emotion Recognition Task. A repeated measures ANOVA revealed equal accuracy performances in both groups

(*F*(1,38) = 0.41, *p* = .52). A main effect of emotion (*F*(5,190) = 53.50, *p* < .001) showed that angry and happy faces were most often labelled correctly, whereas sad and fearful faces were the most difficult to label correctly. Pertaining to the reaction times, again, only a significant main effect of emotion was displayed (*F*(5,190) = 17.60, *p* < .001). Post-hoc tests for the reaction times showed that the reaction times to label happy faces were significantly shorter than the reaction times for all other facial expressions (all *p* < .01). In addition, labelling sad faces took significantly longer than labelling disgust and surprise, and even fear (all *p* < .001). See Supplementary Table S1 for more details.

3.2 Eye tracking

Analysis of the data quality demonstrated no group differences: both groups showed similar average error angles (M_{ASD} = 0.53° ± 0.33; M_{TD} = 0.41° ± 0.21; *t*(32) = 1.30, *p* = .20). The root-mean-square of this angle differed neither (M_{ASD} = 0.70 ± 0.20; M_{TD} = 0.62 ± 0.16; *t*(32) = 1.33, *p* = .19).

3.2.1 Proportional looking times

Both groups of participants spent only a fraction of the time looking outside of the predefined AOIs (M_{ASD} = 11%; M_{TD} = 8%), probably reflecting gaze shifts towards the expression labels aside of the facial stimulus presentation. There was no group difference in the proportional looking times outside of the AOIs (*F*(1,34) = 1.48, *p* = .23).

Pertaining to the gaze points inside the predefined AOIs (eyes, mouth, nose), the LMM only showed a significant main effect of expression (*F*(5,168.71) = 3.17, *p* = .009) and a significant expression x AOI interaction (*F*(10,334.69) = 11.74, *p* < .001). No effect of group nor any interaction effect with group was present (all *p* > .23). This generally implies that the participants present emotion specific gaze patterns, but these are similar for individuals of the ASD and TD groups (Fig. 1 and Supplementary Table S2). The following observations can be deduced. First, post-hoc tests revealed that children with and without ASD looked significantly longer to fearful (*t*(168) = 3.44, *p* = .009) and sad (*t*(169) = -2.89, *p* = .04) faces, as compared to happy faces. Second, when examining face scanning patterns per emotion, we found that the proportional looking times to the eyes were significantly higher than those to the mouth or nose for angry ($t(97.2)_{\text{eyes-mouth}}$ = 2.90, $t(96.6)_{\text{eyes-nose}}$ = 2.60, all *p* < .05) and sad faces ($t(96.6)_{\text{eyes-mouth}}$ = 2.50, $t(95.9)_{\text{eyes-nose}}$ = 2.78, all *p* < .05). For happy faces, we found the reversed effect: here, children spent more time looking at the mouth than the eyes (*t*(96.6) = -2.64, *p* < .05) and nose (*t*(97.2) = 3.18, *p* = .006). The mouth was also significantly more inspected than the nose (*t*(95.9) = 2.91, *p* = .01) when surprised facial expressions were presented (see Fig.1). For further evaluation of this interaction effect, see Supplementary Materials S2.

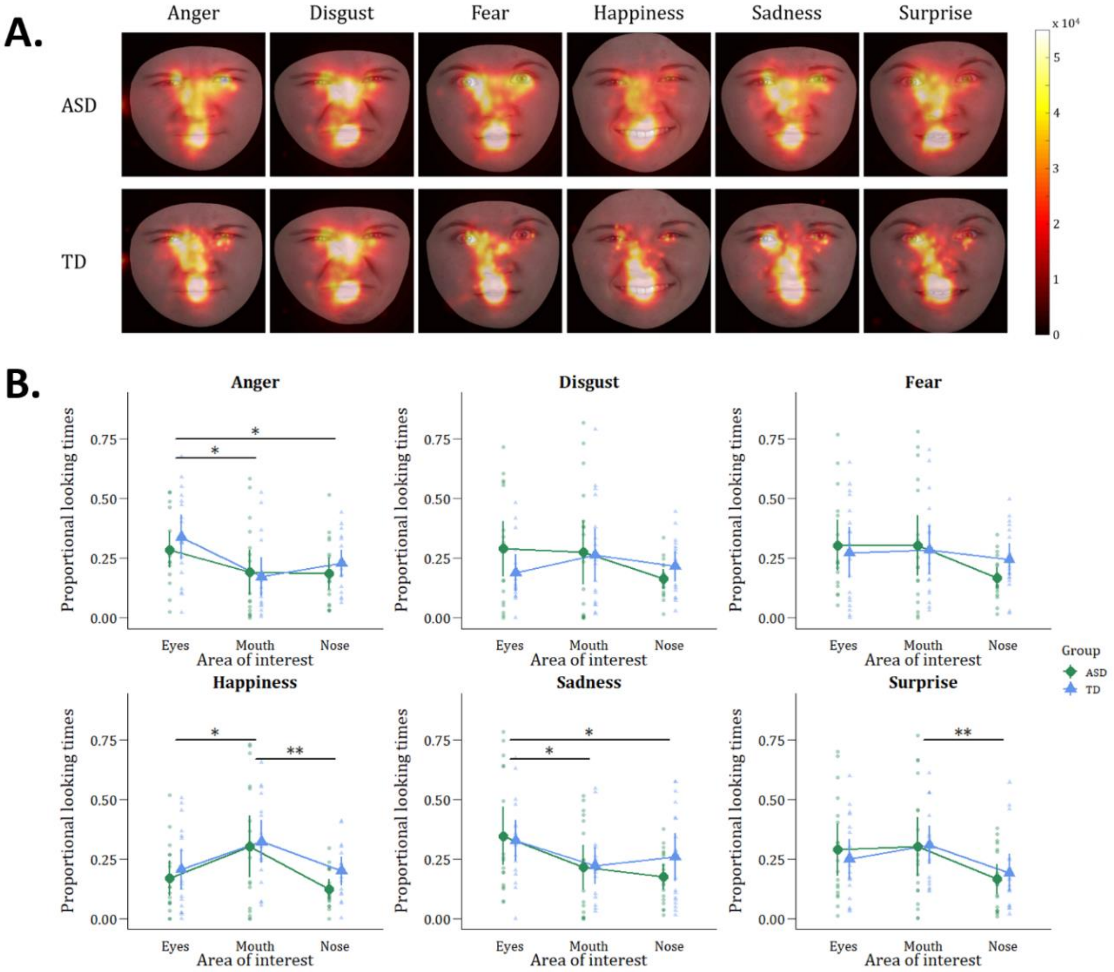


Figure 1. (A) Heat maps of looking time averaged over all participants in the ASD group (upper row) and the TD group (lower row). As indicated by the scale, lighter colors represent longer looking times to that region. (B) The proportional looking times within the face AOIs for the six basic expressions. We plotted the mean and 95% confidence intervals of the proportional looking times in both participant groups. Significant within-expression differences are indicated with asterisks.

3.2.2 Face exploration dynamics

We examined the gaze behavior of the participants in more detail via the number and duration of fixations, as well as the saccadic amplitudes (see Fig.2). The LMM on the **fixation count** data demonstrated significant main effects of AOI (*F*(2,68) = 6.02, *p* = .004) and expression (*F*(5,169.48) = 7.36, *p* < .001), as well as a significant AOI x expression interaction (*F*(10,337.83) = 4.59, *p* < .001) and a significant three-way interaction with group

(*F*(10,337.83) = 2.07, $p < .05$). No other main or interaction effects reached significance (all $p > .08$).

As we are mainly interested in possible group differences of scanning patterns, we broke down the interaction and further inspected the gaze behavior of both participant groups per emotion. We found no group differences in the number of fixations, not in any of the AOIs, nor for any of the facial expressions (all $p > .43$). We did, however, detect significantly more fixations on the eyes versus the mouth and nose when looking at angry ($t(132)_{\text{eyes-mouth}} = 4.15$, $t(132)_{\text{eyes-nose}} = 3.13$, all $p < .05$) and sad ($t(133)_{\text{eyes-mouth}} = 3.28$, $t(133)_{\text{eyes-nose}} = 3.64$, all $p < .05$) faces, but only for TD boys. More details are provided in Supplementary Table S3.

For the **duration of the fixations**, the LMM demonstrated a significant main effect of AOI (*F*(2,67.56) = 6.56, *p* = .002) and expression (F(5,162.82) = 3.39, *p* = .006), further qualified by their significant interaction (*F*(10,268.88) = 5.93, $p < .001$). No other main or interaction effects reached significance (all $p > .11$). Post-hoc tests identified significantly prolonged fixations for all participants on the mouth versus the eyes in four out of the six basic expressions: disgust ($t(163) = -2.58$, $p = .03$), fear ($t(139) = -2.82$, $p = .02$), happiness ($t(160) = -5.90$, $p < .001$) and surprise ($t(150) = -3.12$, $p = .006$). Furthermore, for fearful and happy expressions, the fixations on the mouth also lasted significantly longer than fixations on the nose ($t(164)_{\text{fear}} = 2.77$, $p = .02$; $t(187)_{\text{happiness}} = 4.15$, $p < .001$). See Supplementary Table S4 for more details.

Finally, the LMM on the **saccadic amplitudes** only yielded a significant main effect of group (*F*(1,197.08) = 10.01, *p* = .002), demonstrating that expressive faces in general elicited significantly higher saccadic amplitudes in TD boys (M = 3.97° ± 1.85), as compared to boys with ASD (M = 3.60° ± 2.05).

In sum, across the three fixation measures, boys with and without ASD only differed in their saccadic amplitudes when looking at expressive faces (Fig.2). There were no group differences in the number or duration of fixations on specific facial features. Within the TD group, however, specific facial expressions elicited different gaze behavior in terms of the number of fixations.

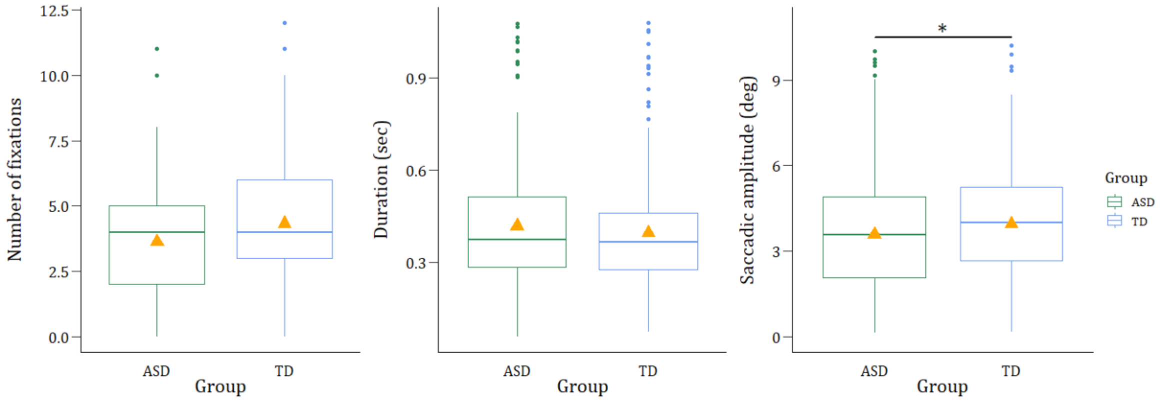
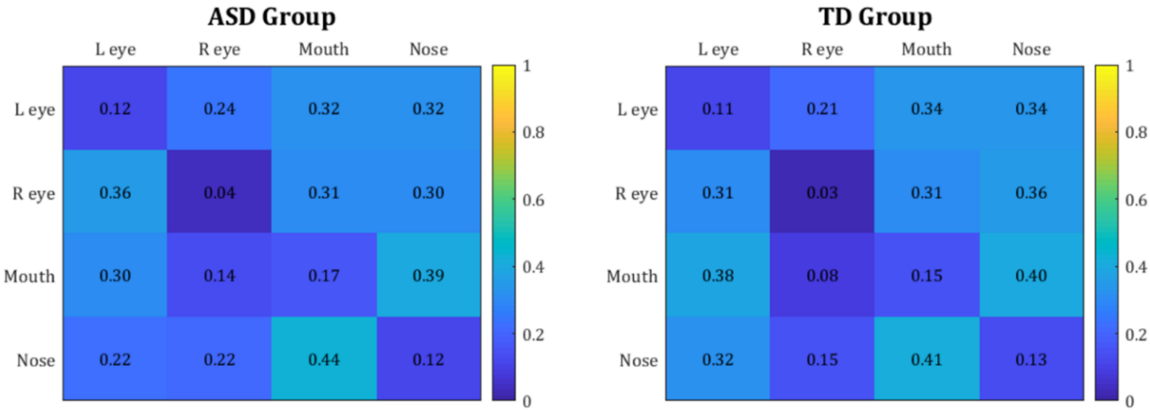


Figure 2. Boxplots of the three fixation measures (from left to right): number of fixations, fixation duration and saccadic amplitudes for both groups, averaged across all facial expressions and all AOIs. The boxes extend from the lower to the upper quartile values, with the median of each group represented by the lines. Mean values are displayed in orange. Note the differences in Y-axis scaling.

As is clearly depicted in the heat maps (fig.1A), both children with and without ASD look at all facial features and to a similar extent. However, the groups might differ in the way they temporally inspect expressive faces, which cannot be inferred from these data. Although there were no significant quantitative differences in the gaze behavior of boys with ASD and TD boys, aside from larger saccadic amplitudes in the TD group, qualitative differences in face exploration strategies might remain concealed. Therefore, the transition matrices add to our understanding of the dynamic face exploration pattern.

Fig.3 shows the average transition matrices (across all expressions) of the OMM models for the ASD and TD group. Note that these transition matrices are strikingly similar across both groups. As can be observed from the very low probabilities of the elements along the diagonal, both boys with and without ASD tend to switch their gaze from one AOI to another. This is not surprising: as participants were explicitly asked to label the presented facial expressions, we would expect them to scan the faces in order to make their choice. The dynamic face exploration patterns of both groups started on average mostly in the left eye AOI (from the viewer's perspective), which is also a region with a high probability to transition to from any of the other AOIs. On the contrary, the right eye AOI shows the lowest transition probabilities – which can also be observed in fig.1A – irrespective of the location of the previous fixation. When boys with ASD and TD boys do fixate on the right eye AOI, they quickly shift their gaze, mainly back to the left eye, or further down to the nose, respectively.

Even though saccadic amplitudes were significantly larger in the TD group in comparison to the ASD group (Fig.2), children from both groups transitioned equally from the eye region to either the mouth or the nose AOI, indicating that fixations not necessarily pass through the nose region first, before reaching the mouth. A similar effect was found when transitioning upwards from the mouth to the eyes and nose. Yet, when fixating on the nose, the gaze shifts seem to go downwards, with the highest probabilities of transitioning to the mouth.


ASD Group

	L eye	R eye	Mouth	Nose
L eye	0.12	0.24	0.32	0.32
R eye	0.36	0.04	0.31	0.30
Mouth	0.30	0.14	0.17	0.39
Nose	0.22	0.22	0.44	0.12

TD Group

	L eye	R eye	Mouth	Nose
L eye	0.11	0.21	0.34	0.34
R eye	0.31	0.03	0.31	0.36
Mouth	0.38	0.08	0.15	0.40
Nose	0.32	0.15	0.41	0.13

Figure 3. *Average transition matrices across all facial expressions for each of the participant groups. The values in each cell represent the probability of looking at the column AOI after having looked at the row AOI. The very low values in the diagonal elements indicate the small chance of maintaining subsequent fixations in the same AOI.*

Thus, both groups displayed a very similar dynamic exploratory face scanning pattern, when explicitly processing expressive faces. When statistically testing for group differences, the MANOVA analysis on the resulting PCA components confirmed that there were no significant differences in exploratory gaze behavior between boys with ASD and TD boys (*F*(8,26) = .081, *p* > .6).

3.3 Facial mimicry

At a more exploratory level, we investigated the spontaneous facial responses of the children while they processed the expressive face stimuli. As an index of facial mimicry, we would expect that a particular displayed expression would elicit a particular and distinctive pattern of produced facial expressions in the children, with higher intensities for produced facial expressions that are congruent with the displayed expressive stimulus. In other words, an interaction between displayed and produced expression would be indicative of the presence of spontaneous facial mimicry in the participants.

The LMM investigating the intensity of the facial responses revealed a significant main effect of produced facial expression (*F*(5,225.41) = 67.06, *p* < .001), a marginally significant interaction between group and produced facial expression (*F*(25,903.48) = 2.09, *p* = .06), but no other main nor interaction effects (all p > .22). Given the non-significant interaction between the displayed and the produced facial expressions, these results suggest the absence of facial mimicry in both participant groups. This interpretation is also supported by the high and dominant intensity of the “neutral” expression in response to any displayed expression (see Fig. 4; note that this neutral expression was not included in the LMM analysis). Accordingly, no additional LMM was performed to investigate potential group differences in the timing of the peak of the produced facial expressions.

Further post-hoc comparisons on the intensity data showed that any displayed expression generally elicited a sad expression in the participants (the intensity of sadness was higher than any of the other produced expressions, all $p < .001$), and certainly not an angry expression (the intensity of anger was lower than any of the other produced expressions, all $p \leq .001$). When inspecting the marginally significant group by produced expression interaction effect, we only uncovered a slightly higher intensity of sad expressions in the ASD group versus the TD group ($t(198) = 1.96$, $p = .05$).

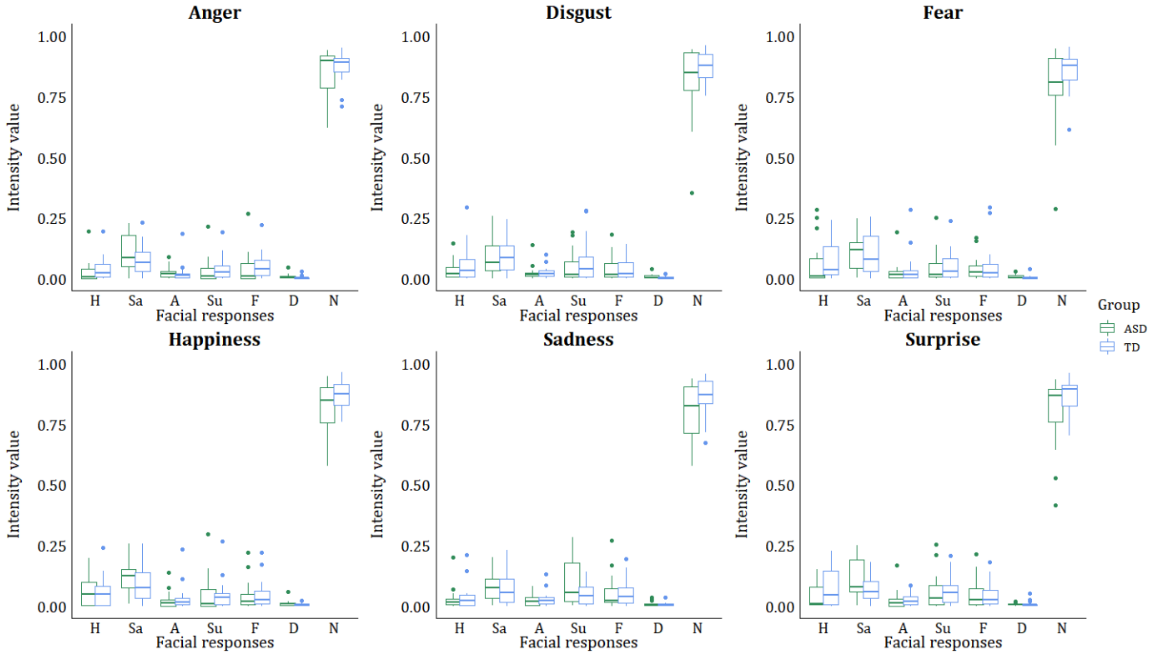


Figure 4. Boxplots representing the intensity values of all facial responses of TD children (blue) and children with ASD (green) for the different stimuli (i.e. 6 basic expressions), indicating very little facial responses to expressive facial stimuli and even fewer facial mimicry. The boxes extend from the lower to the upper quartile values, with the median of each group represented by the lines. Note, the neutral facial expression of the participants was not included in the LMM analysis. H = happy, Sa = sad, A = angry, Su = surprised, F = fearful, D = disgusted and N = neutral.

4. Discussion

Emotional face processing has been investigated in numerous behavioral studies with individuals with ASD, yielding, however, mixed and inconsistent results (Harms, 2010; Uljarevic, 2013). Difficulties with facial expression recognition might remain concealed on a behavioral level due to the use of compensatory strategies. Therefore, administration of tasks tapping automatic implicit emotion processing is needed (Rutherford, 2007). Indeed, in previous studies using implicit frequency-tagging EEG paradigms, we found a significantly reduced neural sensitivity for specific emotions in boys with ASD as compared to TD boys (Van der Donck, 2020, 2019), in spite of equal behavioral emotion recognition accuracy. Therefore, to gain more insight in automatic affective processes underlying facial emotion processing, we combined an explicit behavioral measure with two implicit measures: eye tracking and facial mimicry recordings.

4.1 Proportional looking times reflect behavioral emotion recognition performances

Behavioral performance on the Emotion Recognition Task was comparable to the results obtained in the previous study: there were no group differences in terms of accuracy nor reaction times to label the expressions, and children of both groups labeled sad and fearful faces less accurately (and more slowly) as compared to angry and happy faces. This difficulty with these particular emotions was also reflected in the proportional looking times measured via eye tracking, as participants looked significantly more to sad and fearful faces, as compared to happy faces. This is not surprising: time spent looking at stimuli typically increases with increasing task difficulty (Del Bianco et al., 2018). As happiness is recognized the earliest and easiest, needing only minimal signals (Whitaker, 2017), this emotion requires less inspection time to be labeled correctly.

4.2 TD boys adapt their gaze behavior more in function of the displayed expression

No group differences were observed in terms of proportional looking time to any of the AOIs nor for any of the emotions. When zooming in on more specific gaze characteristics such as number and duration of fixations and saccadic amplitude, we only found a significant group difference for the saccadic amplitudes, with higher amplitudes in the TD group as compared to the ASD group. However, a closer look at the significant three-way group by AOI by expression interaction for the number of fixations revealed subtle differences in fixation behavior. More specifically, TD boys fixated more on the eyes versus the nose and mouth for angry and sad faces, and more on the mouth when viewing happy and surprised facial expressions. These results are in line with previous findings showing increased fixations on the eyes when viewing negative emotions, while fixating more on the mouth during the presentation of positive emotions (Eisenbarth, 2011; Wagner et al., 2013; Wegrzyn, 2017). However, this emotion by AOI interaction was only significant in the TD group and not in the ASD group. These findings suggest that TD boys adapt their gaze pattern in relation to the emotional content of the faces (Åsberg Johnels, 2017; Beaudry, 2014), probably by actively orienting towards the most informative face region displaying the most characteristic changes when evolving from neutral to expressive.

4.3 Similar face exploration dynamics, with a little more visual persistence in ASD

The classical eye tracking measures described above generally revealed very similar face scanning behavior between boys with and without ASD, with only a significant group difference for saccadic amplitudes, and a somewhat reduced flexibility in adopting the most optimal gaze behavior in ASD. Likewise, also the observable Markov models, probing the individual temporal patterns and the fixation transition matrices, demonstrate that both groups employ similar face exploration dynamics. Children from both groups seem to dynamically shift their gaze across all AOIs when recognizing facial expressions, with a lower frequency of fixation on the right eye.

The observation that the first fixations of participants from both groups were generally directed towards the left eye, as seen from the viewer's perspective, resonates with previous accounts of a left-eye bias -and thus right-hemisphere advantage- in (emotional) face processing (Voyer et al., 2012; Wirsen et al., 1990). In addition to starting fixating on the left eye, children of both groups also looked more to this AOI and showed a higher probability to turn their gaze there, as opposed to the right eye. Whereas some studies failed to find this left-eye bias in individuals with ASD (Ashwin et al., 2005; Dundas et al., 2012; Guillon et al., 2015), a meta-analysis revealed no differences between TD individuals and individuals with ASD in demonstrating this bias (Voyer, 2012).

If anything, the significant group difference for the saccadic amplitudes, with lower amplitudes in boys with ASD versus TD boys, suggests a less exploratory visual strategy to recognize the expressions in boys with ASD. Saccade amplitudes can be interpreted as a measure of visual exploration: smaller amplitudes demonstrate a tendency to fixate on locations that are near to the previous ones, higher amplitudes imply larger jumps to the next location (Vabalas, 2016). However, image size and mean saccadic amplitude are linearly related (Von Wartburg et al., 2007). Therefore, in light of the 9.93° visual angle that the stimuli subtend, a saccadic amplitude difference of 0.4° between the two participant groups is a relatively small difference. Nevertheless, these results indicate that boys with ASD tend to fixate on locations that are near to the previous one, whereas TD boys shift their gaze across wider distances. In combination with the modelling of the temporal scanning dynamics, these saccadic amplitudes suggest a slightly less exploratory and a slightly more persistent processing strategy in boys with ASD. The lower saccadic amplitudes recorded in the ASD group may encompass a more detail-focused visual exploration strategy in local areas (Heaton & Freeth, 2016; Vabalas, 2016), which aligns with the slightly higher reliance on individual facial features during implicit facial emotion processing and possibly aids the rule-based emotion recognition (i.e. compensatory mechanism).

4.4 Lack of facial mimicry, but similar facial responses in boys with and without ASD

We also explored the facial mimicry of the participants while they were explicitly recognizing the displayed dynamic facial expressions. Although not the focus of this study, we generally found a low expression intensity (i.e. presence) of anger during the task, and an overall higher intensity of sadness, which was even slightly higher in the ASD group as compared to TDs. Without refuting that our participants might indeed have mostly displayed a sad facial expression throughout the experiment, we prefer to rather cautiously interpret these results, as FaceReader has previously been found to measure high levels of sadness, when other measures (e.g. EMG) did not (Suhr, 2017). In the present experiment, we assume that the particular camera angle might have induced FaceReader to mistakenly decode neutral faces as sad faces.

Most importantly in light of our interest, the results from the FaceReader analysis indicated the absence of facial mimicry in each of the groups. As can be clearly observed in Fig.4, the intensity values of all expressions are very low, except for the neutral facial expression. This combination of high neutral scores and low expressive scores indicates little variation in the participants' facial expressions, and, accordingly, no mapping between the observed and produced facial expressions. Thus, while the absence of a group difference aligns with the findings of a recent meta-analysis (Trevisan, 2018), we believe that our facial mimicry data are not informative in this matter. Indeed, given the overall very low emotional expression intensities, we conclude that the Emotion Recognition Task did not elicit clear facial responses, hence, might not have been suited to investigate spontaneous facial mimicry. Possibly, the duration of the video clips was too short. However, previous studies investigating facial mimicry in children and adults with ASD presented expressive facial stimuli for one or two seconds and did find clear facial responses to the stimuli (Oberman, 2009; Schulte-Rüther, 2017). Yet, these studies applied EMG, which may be a more sensitive approach to detect even the subtlest changes in the facial muscles. Moreover, future studies should apply more evocative expressive stimuli, preferably within the context of real-life dyadic social interactions.

5. Conclusions

Our results indicate that boys with and without ASD employ similar eye gaze strategies to recognize facial expressions. However, the larger saccadic amplitudes in TD boys, are suggestive of a less exploratory face processing strategy in boys with ASD. Yet, the slightly more persistent visual scanning behavior in boys with ASD, does not impede the processing of emotional information from the faces, as is evident from their equal behavioral emotion recognition performances.

In addition, results on the facial mimicry data indicate similar facial responses to emotional faces in boys with and without ASD.

6. Supplementary materials

S1. Explicit facial expression recognition

Table S1. Behavioral accuracy and reaction times

	Accuracy Mean % (SD)		Reaction time Mean sec (SD)	
	ASD	TD	ASD	TD
Anger	78.75 (20.32)	77.50 (25.52)	6.99 (4.86)	5.63 (2.37)
Disgust	61.25 (33.91)	70.00 (25.13)	4.69 (2.47)	5.50 (2.05)
Fear	40.00 (27.39)	33.75 (27.24)	5.42 (2.13)	5.76 (1.71)
Happiness	91.25 (16.77)	91.25 (18.63)	3.07 (0.96)	3.73 (1.62)
Sadness	21.25 (20.32)	18.75 (21.27)	7.65 (3.49)	7.50 (2.65)
Surprise	45.00 (28.79)	61.25 (18.98)	5.26 (1.89)	5.51 (2.63)

Average accuracy and reaction times (and standard deviations) for both groups when explicitly recognizing the six basic expressions during the Emotion Recognition Task.

S2. Proportional looking times

Table S2. Proportional looking times

	Eyes Mean % (SD)		Nose Mean % (SD)		Mouth Mean % (SD)	
	ASD	TD	ASD	TD	ASD	TD
Anger	29 (15)	34 (19)	19 (14)	23 (11)	19 (19)	17 (16)
Disgust	29 (23)	19 (14)	16 (8)	22 (12)	27 (27)	26 (22)
Fear	30 (21)	27 (21)	17 (9)	24 (13)	30 (25)	28 (21)
Happiness	17 (14)	21 (17)	12 (8)	20 (12)	30 (26)	32 (18)
Sadness	35 (25)	33 (17)	17 (11)	26 (20)	21 (19)	22 (15)
Surprise	29 (22)	25 (17)	16 (13)	19 (16)	30 (25)	31 (16)

Average proportional looking times (and standard deviation (SD)) for both groups, for all six basic expressions and all three areas of interest.

The significant interaction between AOI and expression – described in the main text – was also demonstrated at the AOI level. In particular, here, we found significantly reduced looking times to the eyes for happy faces as compared to the other five facial expressions ($t(498)_{\text{anger-happiness}} = 6.20$, $t(499)_{\text{disgust-happiness}} = 3.21$, $t(498)_{\text{fear-happiness}} = 5.21$, $t(498)_{\text{happiness-sadness}} = -7.19$, $t(498)_{\text{happiness-surprise}} = -3.71$, all $p < .05$). In addition, children looked proportionally more to the eyes of sad faces in comparison to disgusted ($t(498) = -3.81$, $p = .002$) and surprised faces ($t(498) = 3.51$, $p = .006$). Furthermore, gazes of all children were directed significantly less to the mouth when looking at angry faces versus disgusted ($t(498) = -3.97$, $p = .001$), fearful ($t(498) = -5.26$, $p < .001$), happy ($t(498) = -6.22$, $p < .001$) or surprised ($t(498) = -5.80$, $p < .001$) faces. A similar effect was displayed for sad faces when compared to fearful ($t(498) = 3.39$, $p < .01$), happy ($t(498) = 4.36$, $p < .001$) or surprised ($t(498) = -3.93$, $p = .001$) facial expressions.

S3. Number of fixations

Table S3. Number of fixations

	Eyes Mean (SD)		Nose Mean (SD)		Mouth Mean (SD)	
	ASD	TD	ASD	TD	ASD	TD
Anger	4.31 (1.89)	6.28 (2.78)	3.17 (1.54)	3.89 (1.53)	3.22 (2.67)	3.11 (1.91)
Disgust	4.44 (3.17)	5.28 (3.48)	3.06 (1.70)	4.22 (1.73)	3.11 (2.40)	3.39 (1.85)
Fear	5.06 (2.94)	4.76 (3.05)	3.28 (1.45)	4.72 (1.71)	4.00 (2.45)	4.06 (1.89)
Happiness	3.18 (1.85)	4.00 (2.83)	2.56 (1.34)	3.44 (2.01)	3.00 (1.88)	3.89 (1.60)
Sadness	5.00 (2.26)	6.56 (2.94)	3.44 (1.72)	3.78 (2.51)	3.22 (2.46)	4.06 (1.98)
Surprise	4.33 (2.66)	4.83 (3.17)	3.33 (2.09)	3.11 (1.94)	3.72 (2.35)	4.72 (1.41)

Average number of fixations (and standard deviation (SD)) for both groups, for all six basic expressions and all three areas of interest.

In addition to what was described in the main text, the interaction effect also revealed that within the eye region, the ASD group displayed significantly more fixations during the presentation of fearful and sad faces, as compared to happy faces ($t(505)_{\text{fear-happiness}}$ = 3.53, $t(505)_{\text{happiness-sadness}}$ = -3.69, all $p < .05$). TD boys, on the other hand, fixated more on the eyes when sad faces were presented in comparison to fearful ($t(505) = -3.53$, $p = .03$), happy ($t(505) = -5.63$, $p < .001$) and surprised ($t(505) = 3.80$, all $p = .01$) faces. Furthermore, the mouth and nose region were fixated more by TD boys when looking at surprised faces, as compared to angry ($t(505) = -3.55$, $p = .03$) and fearful faces ($t(505) = 3.55$, $p = .03$), respectively.

S4. Fixation duration

Table S4. Fixation duration

	Eyes Mean sec (SD)		Nose Mean sec (SD)		Mouth Mean sec (SD)	
	ASD	TD	ASD	TD	ASD	TD
Anger	0.39 (0.14)	0.32 (0.09)	0.34 (0.16)	0.42 (0.21)	0.37 (0.15)	0.40 (0.23)
Disgust	0.42 (0.09)	0.32 (0.07)	0.33 (0.09)	0.39 (0.21)	0.43 (0.18)	0.45 (0.25)
Fear	0.38 (0.15)	0.33 (0.12)	0.35 (0.18)	0.37 (0.18)	0.51 (0.24)	0.49 (0.19)
Happiness	0.34 (0.11)	0.30 (0.10)	0.33 (0.14)	0.43 (0.17)	0.68 (0.28)	0.54 (0.19)
Sadness	0.37 (0.13)	0.35 (0.09)	0.32 (0.13)	0.37 (0.17)	0.46 (0.24)	0.37 (0.15)
Surprise	0.47 (0.23)	0.36 (0.14)	0.30 (0.21)	0.48 (0.28)	0.48 (0.27)	0.51 (0.24)

Average fixation duration (and standard deviation (SD)) in seconds for both groups, for all six basic expressions and all three areas of interest.

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Part III

To sniff or not to sniff?

Chapter 5

Monitoring the effect of oxytocin on the neural sensitivity to expressive faces via frequency-tagging EEG

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Under review in *Psychoneuroendocrinology*.

Abstract

The neuropeptide oxytocin (OXT) is suggested to exert an important role in human social behaviors by modulating the salience of social cues. To date, however, there is mixed evidence whether a single dose of OXT can improve the behavioral and neural sensitivity for emotional face processing. To overcome difficulties encountered with classic event-related potential studies assessing stimulus-saliency, we applied frequency-tagging EEG to implicitly assess the effect of a single dose of OXT (24 IU) on the neural sensitivity for positive and negative facial emotions. Neutral faces with different identities were presented at 6 Hz, periodically interleaved with an expressive face (angry, fearful, and happy, in separate sequences) every fifth image (i.e. 1.2 Hz oddball frequency). These distinctive frequency tags for neutral and expressive stimuli allowed direct and objective quantification of the neural expression-categorization responses. The study involved a double-blind, placebo-controlled, cross-over trial with 31 healthy adult men. We did not find an overall effect of OXT on facial emotion processing, yet, a significant moderation of the OXT treatment effect was evident, indicating a complex modulation of neural sensitivity, depending on person-dependent factors, as well as facial expression valence. Particularly, while participants with more social problems initially displayed a higher neural sensitivity for angry faces (at baseline), a single dose of OXT was shown to specifically attenuate these responses in individuals with high baseline sensitivity. No significant modulation was revealed for happy or fearful faces. Overall, our pattern of results points towards a modulation of OXT treatment responses depending on person-dependent factors (level of social proficiency) and contextual factors (valence of facial expressions), suggesting that in certain subpopulations, OXT can attenuate the neural sensitivity towards angry faces.

1. Introduction

Being able to quickly and adequately read faces and facial expressions is a key component for successful everyday social interactions, as it allows for understanding one's feelings, reactions and intentions (Elfenbein and Ambady, 2002). Moreover, proficient recognition of emotional faces has been found to be related to more prosocial behavior (Kaltwasser et al., 2017).

An important biological modulator of prosocial behavior and socio-cognitive processes is endogenous oxytocin (OXT; MacDonald and MacDonald, 2010). OXT is a neuropeptide that is produced in the hypothalamus and functions as a hormone and neuromodulator (Wigton et al., 2015). Central OXT levels can, however, be manipulated by intranasally administered exogenous OXT (Quintana et al., 2018), which encouraged numerous researchers over the past decades to study the effect of OXT on human sociality. Generally, it has been thought to invariantly improve prosocial behavior and social cognition, yet, reviews have demonstrated its variable nature and the importance of individual differences and the social context (Bartz et al., 2011; Evans et al., 2014). For instance, effects of exogenous OXT have mainly been observed in those individuals who initially (i.e. before OXT treatment) scored low in terms of social-cognitive competence (Bartz et al., 2010).

Mechanistic models suggest that OXT may exert its complex 'prosocial' effects by regulating the saliency of social cues and/or by modulating (social) stress and anxiety (Churchland and Winkielman, 2012; Shamay-Tsoory and Abu-Akel, 2016), which can be of particular interest for facial emotion recognition. Indeed, many behavioral studies have sought to elucidate how OXT affects facial expression processing. Despite the overall notion of OXT enhancing emotion recognition, closer inspection of the findings reveals rather attenuated and inconsistent results (for reviews and a meta-analysis, see Evans et al., 2014; Leppanen et al., 2017; Shahrestani et al., 2013; Van IJzendoorn and Bakermans-Kranenburg, 2012). Whereas some studies found an overall improvement of facial expression recognition, irrespective of the valence of the expressions (Guastella et al., 2010; Lischke et al., 2012), others have reported an OXT effect for positive (Di Simplicio et al., 2009; Schulze et al., 2011) or negative (Fischer-Shofty et al., 2010) emotions only. In a similar vein, OXT has been found to modulate approach-avoidance motivational tendencies, by facilitating sensitivity for positive emotional stimuli (Kemp and Guastella, 2011) and attenuating sensitivity for negative emotional stimuli (Ellenbogen, 2018). Moreover, some studies showed that the OXT induced improvement was dependent on task difficulty (Guastella et al., 2010).

Effects of a single dose of OXT on emotion recognition have also been investigated at the neural level, mostly using functional magnetic resonance imaging (fMRI). These studies commonly showed attenuated amygdala activity, mostly in response to negative social stimuli (for meta-analyses, see Grace et al., 2018; Wang et al., 2017), which is considered to reflect a reduction in social anxiety. Yet, similar to the behavioral data, results vary and point into different directions. For example, while attenuated amygdala activity has been reported during implicit and explicit processing of both positive (Domes et al., 2007) and negative (Domes et al., 2007; Gamer et al., 2010) emotions, enhanced amygdala activity for happy faces has also been reported (Gamer et al., 2010). Furthermore, in women, a single dose of OXT enhanced activity in different brain regions in relation to specific facial emotions (Domes et al., 2010): increased activation for angry faces was reported in the inferior frontal gyrus and ventro-lateral prefrontal regions, for happy faces in the inferior frontal gyrus and the fusiform gyrus, and for fearful faces in the medial and superior temporal cortex and the bilateral fusiform gyrus. In addition, OXT also augmented functional connectivity between the amygdala and the reward system (Wang et al., 2017) or the salience network (Grace et al., 2018; Wang et al., 2017). Moreover, a recent meta-analysis proposed increased activity in the superior temporal gyrus resulting from OXT administration as the main factor for improved emotion recognition (Grace et al., 2018).

To date, few studies have investigated the effects of a single dose of OXT on facial emotion processing using electroencephalography (EEG). Recently, event-related potential (ERP) studies investigating the modulatory effect of OXT reported shorter latencies of the N170 component (Tillman et al., 2019), as well as increased amplitudes of the N170 (Peltola et al., 2018) and the vertex positive potential (VPP; (Huffmeijer et al., 2013)), indicating enhanced sensitivity and improved neural efficiency to process emotional faces. Yet, results were inconsistent for the late positive potential (LPP): some studies reported OXT-induced increases in LPP amplitudes (Huffmeijer et al., 2013), whereas others reported no effects of OXT on this component (Peltola et al., 2018). Possibly, differences in task demands, or differently chosen time windows to capture the ERP components might account for the contrasting findings across studies, as selecting specific time windows to accurately measure the ERP component(s) of interest is one of the most challenging aspects of classic ERP studies (Kappenman and Luck, 2016). In addition, the low signal-to-noise ratio (SNR) of ERP measurements requires many trials, resulting in long EEG recordings.

1.1 Present study

Given the challenges of classic ERP research, here, we applied a relatively novel approach to investigate the modulatory effect of a single dose of OXT on facial expression processing: frequency-tagging EEG. Frequency-tagging EEG relies on the principle that brain activity synchronizes to a periodically flickering stimulus (Adrian & Matthews, 1934) and elicits a brain response at exactly the same frequency of stimulation (Norcia et al., 2015). Similar to previous studies (Dzhelyova et al., 2017; Van der Donck et al., 2020), we applied this principle in a facial expression oddball paradigm, by periodically interleaving a rapidly presented stream of neutral faces with expressive faces. The neutral faces act as forward and backward masks for the expressive faces, allowing us to selectively isolate the sensitivity to the expressions by putting the emotional face processing system under tight temporal constraints, without the influences of mechanisms other than fast and automatic emotion extraction. The periodic presentation at predefined, yet, different, frequency rates generates distinguishable frequency tags for the base and oddball stimuli, allowing direct quantification of the neural responses, indicating the discrimination of expressive faces amongst neutral faces. This makes frequency-tagging EEG a highly objective measure. In addition, the rapid presentation enables a fast acquisition of many neural responses indexing expression discrimination in only a few minutes of recording, with a high SNR. Previous research showed that frequency-tagging oddball paradigms have a high test-retest reliability (Dzhelyova et al., 2019) and are able to sensitively pinpoint differences in facial expression processing (Van der Donck et al., 2020, 2019), making them highly suited to monitor subtle changes in facial expression sensitivity, as for example induced by intranasal OXT administration.

Accordingly, in the present study, we investigated the prosocial effect of a single dose of OXT on the neural sensitivity to brief changes in facial expression. We included angry, fearful, and happy faces as oddball stimuli in rapidly presented streams of neutral faces, in order to monitor possible modulatory effects on both positive and negative facial expressions. To prevent expression discrimination based on low-level visual features, we continuously changed the identity of the faces (i.e. every image). Thirty-one healthy adult men participated in a double-blind, placebo-controlled, cross-over trial, where they randomly received either a single dose of OXT or placebo during test sessions with a two-week interval. In addition to the EEG measures, we administered a behavioral facial expression matching task and a questionnaire assessing social responsiveness.

Following the social salience hypothesis (Shamay-Tsoory and Abu-Akel, 2016), we might expect to find an overall salience effect of OXT, reflected in enhanced neural responses to facial expressions in general, irrespective of emotion. However, in line with the inconsistencies in the OXT literature (Bartz et al., 2011; Evans et al., 2014; Shahrestani et al., 2013), we anticipated a potential modulation of the OXT treatment response depending on context (expression valence) and possibly person-dependent factors. Specifically, and in line with evidence (Domes et al., 2013; Ellenbogen, 2018; Xu et al., 2015) supporting the social approach/withdrawal hypothesis (Kemp and Guastella, 2011), we expect OXT to selectively attenuate the attentional bias for negative facial stimuli and enhance the neural sensitivity for positive facial stimuli. Moreover, as person-dependent factors, such as social responsiveness, have been found to moderate the prosocial effects of OXT (Bakermans-Kranenburg and Van IJzendoorn, 2013; Shamay-Tsoory and Abu-Akel, 2016), we explored whether inter-individual differences in person-dependent factors also modulated OXT treatment effects on the neural sensitivity for facial emotions. Based on the existing literature, we expect to find a larger OXT treatment effect, reflected in an enhanced modulation of neural sensitivity to discriminate expressive faces, in participants reporting more social difficulties (Bartz et al., 2010; Bartz et al., 2011).

2. Material and methods

2.1 Participants

Thirty-one healthy right-handed male participants, aged between 18 and 32 years (mean age = 22.81 years, SD = 2.38 years), were included in this study. Only male participants were recruited in order to avoid possible gender differences in response to OXT administration (Domes et al., 2010) and in facial emotion processing (Kret and De Gelder, 2012). In addition to gender, age (18-35 years old) and right-handedness, inclusion criteria further comprised the absence of any diagnosed psychiatric, neurological or genetic disorders in the participant or a first-degree relative. All participants had a normal or corrected to normal vision. One participant reported color blindness, but as he had no difficulties detecting the color changes of the fixation cross, he was not excluded.

At the beginning of the first session, participants completed a self-report questionnaire allowing us to evaluate inter-individual treatment-effects related to person-dependent factors: the Social Responsiveness Scale for Adults (SRS-A; Noens et al., 2012). The SRS-A is a 64-item questionnaire using a four-point Likert-scale to assess the participant's interpersonal and repetitive behavior according to four subscales: social awareness, social communication, social motivation and rigidity/repetitiveness. Higher scores indicate more social responsiveness difficulties and autism characteristics. As expected, on average, the participants yielded typical general population scores (*T*-scores), confirming the absence of any marked psychopathology (Social Awareness Scale M = 48.35, SD = 8.57; Social Communication M = 48.48, SD = 8.46; Social Motivation Scale M = 48.26, SD = 8.12; Rigidity and Repetitive Behavior M = 52.48, SD = 9.61).

The Medical Ethical Committee of the university hospital approved this study. Written informed consent according to the Declaration of Helsinki was obtained from the participants. Participants received a monetary compensation for their participation. The trial was registered with the ClinicalTrials.gov database of the U.S. National Institutes of Health (NCT03096249).

2.2 Study design

We performed a randomized, double-blind, within-subjects, cross-over, placebo (PL)-controlled study, with the sessions two weeks apart. More specifically, the experiment consisted of two identical test sessions – except for the nasal spray the participants received – that took place at exactly the same time of the day, 14 days apart. Based on random assignment, half of the participants received the OXT spray (Syntocinon®, Sigma Tau) in the first session and the PL spray (saline solution of sodium chloride in water) in the second session. For the other half of the participants, the order was reversed.

2.3 OXT administration

At the start of each session, participants received clear instructions on how to administer the nasal spray themselves (Guastella et al., 2013), applying the widely used single dose of 24 international units (IU) (Graustella and MacLeod, 2012) of OXT via three puffs of 4 IU per nostril. Based on previous studies investigating the time interval between the intranasal administration of a single dose of OXT and increased peripheral OXT levels (Daughters et al., 2015; Striepens et al., 2013), generally, a 30-45 minute wait-time is implemented post-administration (Graustella and MacLeod, 2012). Consequently, in order to test during peak OXT concentrations, we incorporated an interval of 30 minutes between nasal spray administration and the start of the EEG paradigm. Potential side effects or adverse events due to the OXT administration were monitored throughout the entire session (see Appendix Table A.1).

2.4 Procedure

Participants were seated in a dimly lit room at 80 cm viewing distance of an LCD 24-in. computer screen, placed at eye level, on which pictures of facial expressions were presented while recording EEG. During the stimulus presentation, an orthogonal task was implemented to guarantee attentiveness of the participants. A fixation cross, presented on the nasion of the presented faces, briefly (300 ms) changed color from black to red 10 times within every sequence. The participants had to respond as soon and accurately as possible when noticing the color changes. Note that the current study was part of a larger project examining the effect of OXT on neural sensitivity for different subtle socio-emotional cues.

2.4.1 FPVS-EEG paradigm

The design was similar to previous studies (Dzhelyova et al., 2017; Van der Donck et al., 2020). Neutral faces from continuously changing identities (i.e., every image) were displayed through sinusoidal contrast modulation (0%–100%) at a 6 Hz base rate, periodically interleaved with an oddball stimulus displaying an expression every fifth image (6 Hz/5 = 1.2 Hz oddball rate). Each sequence started with a blank screen for a variable duration of 2–5 s. After two seconds of gradually fading in (0%–100%), the images were presented for 60 s, followed by two seconds of gradually fading out (100%–0%). Three conditions were included (i.e., the emotional expressions happiness, anger and fear), and each was presented in a separate sequence and repeated four times, resulting in 12 sequences that were all presented in a randomized order (Fig.1). The facial stimuli varied randomly in size between 80% and 120% of the original size.

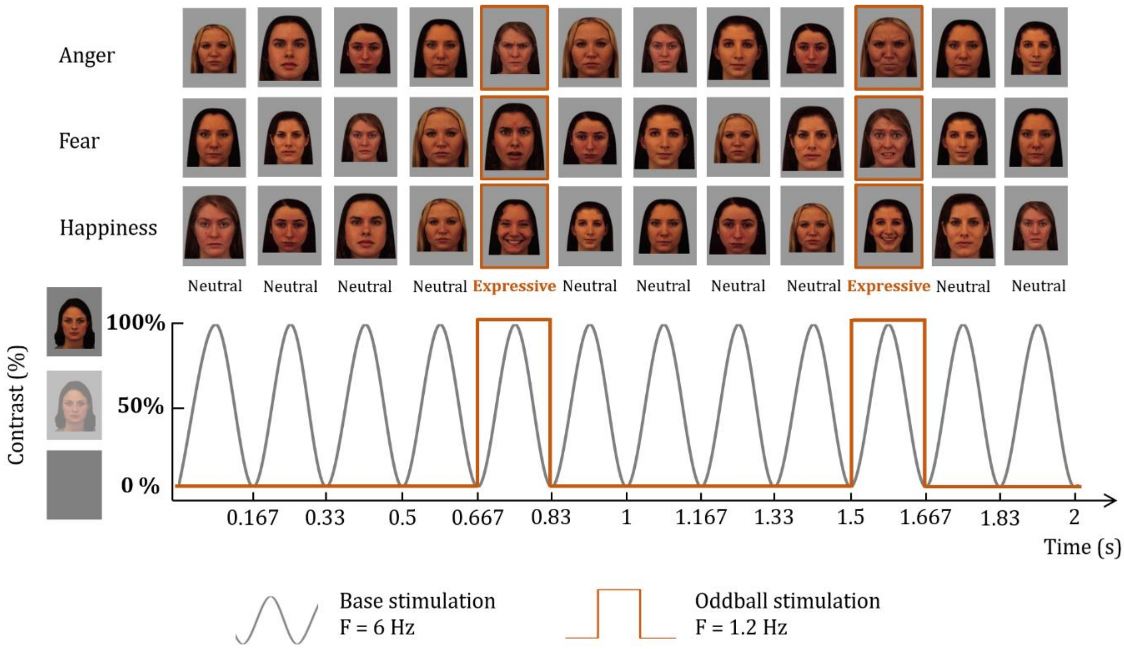

Figure 1. Fast periodic visual stimulation oddball paradigm. Neutral faces are presented sequentially at a fast 6 Hz base rate, periodically interleaved with an expressive face – anger, fear, happiness – every fifth image (1.2 Hz oddball rate). The identity of the faces changes every image. Stimuli shown here: AF02, AF07, AF13, AF15, AF22, AF27, AF29.

2.4.2 Stimuli

The stimuli comprised full-front, full-color images of 14 individuals (seven females, seven males) from the Karolinska Directed Emotional Faces database (Lundqvist et al., 1998), displaying either a neutral, happy, angry or fearful expression. Mean pixel contrast and luminance of the pictures were equalized. The images were set to a size of 300 x 450 pixels, equalizing 2.54° x 3.29° of visual angle, and were placed against a grey background.

2.4.3 EEG acquisition

We recorded EEG activity using a BIOSEMI Active-Two amplifier system with 64 Ag/AgCl electrodes and two additional electrodes as reference and ground electrodes (Common Mode Sense active electrode and Driven Right Leg passive electrode). Vertical eye movements were recorded via one electrode above and one below the right eye. One electrode was placed at the corner of both eyes to record horizontal eye movements. We recorded EEG and electrooculogram at 512 Hz.

2.4.4 EEG analysis

Pre-processing. Pre-processing was performed using 'Letswave6' (http://www.nocions.org/letswave/), a toolbox running in Matlab 2017b (Mathworks). The continuous EEG data were cropped into segments of 70 seconds (4 s before and 6 s after stimulus presentation). We applied a bandpass Butterworth filter (fourth order; 0.1-100 Hz) and resampled the data to 256 Hz. We applied independent component analysis via the runica algorithm (Makeig et al., 1995) for two participants who blinked on average more than 2SD above the mean (average number of blinks per second across participants = 0.10, SD = 0.09) and we removed the component that accounted for most of the variance. Noisy or artefact-ridden channels were re-estimated via linear interpolation using the three spatially nearest, neighbouring electrodes (not more than 5% of the electrodes (i.e. three electrodes) were interpolated). All data segments were re-referenced to a common average reference.

Frequency domain analysis. The pre-processed data segments were then cropped to contain an integer number of 1.2 Hz cycles beginning immediately after the fade-in until approximately 59.22 seconds (72 cycles). After averaging the data in the time domain per condition and for each participant separately, we applied a fast Fourier transformation (FFT), yielding amplitude spectra with a spectral resolution of 0.017 Hz. To obtain a measure of neural sensitivity for facial expressions (Dzhelyova et al., 2017), we calculated baseline-subtracted amplitudes at the oddball frequency and its harmonics (i.e., n*F/5 = 2.4 Hz, 3.6 Hz, etc.), by subtracting the average amplitude level of the 20 surrounding bins from the amplitude of the frequency bin of interest (Retter and Rossion, 2016). These 20 surrounding bins are the 10 bins on each side of the target frequency bin, excluding the immediately neighbouring bins and the two bins with the most extreme values. Baseline-subtracted amplitudes express responses in amplitudes (µV) that can be summed across significant harmonics to quantify the overall base and oddball response (Retter and Rossion, 2016). In addition, we calculated signal-to-noise ratio (SNR; by dividing the amplitude value of the target frequency bin by the average amplitude of the 20 surrounding frequency bins) for visualization, as this allows to visualize even small response amplitudes with high SNR (Rossion et al., 2012).

In order to assess the significance of the responses to define the number of base and oddball harmonics to include in the analyses, Z-scores were calculated using the mean and standard deviation of the 20 frequency bins surrounding the bin of interest (Liu-Shuang et al., 2014). Harmonics were considered significant until the Z-score no longer exceeded 1.64 ($p < .05$), for two consecutive harmonics. Consequently, we quantified the oddball response as the sum of the responses of the first seven harmonics (i.e. until 7F/5 = 8.4 Hz), excluding the 6 Hz general response. The base rate response (i.e. 6 Hz) was quantified as the summed responses of the base rate and its following two harmonics (2F and 3F = 12 Hz and 18 Hz, respectively).

Defining regions of interest (ROIs). Previous research using similar frequency-tagging facial expression processing EEG paradigms (Dzhelyova et al., 2017; Van der Donck et al., 2019; 2020) has consistently identified three regions to be the most responsive for emotion discrimination as assessed by oddball stimulation. Likewise, also in the present study, the highest oddball responses – capturing all relevant oddball activity, as can be seen in Fig. 3 – were measured over these left and right occipito-temporal (LOT and ROT region) and medial-occipital (MO region) sites. Accordingly, region-of-interest (ROI) analyses were performed to examine OXT-treatment effects within these regions by averaging the summed baseline-subtracted oddball responses over channels P7, P9, and PO7 for the LOT region, over channels P8, P10, and PO8 for the ROT region and over channels Iz and Oz for the MO region (see Fig.2).

While the 1.2 Hz oddball response reflects the strength of neural expression discrimination, the 6 Hz base rate response reflects the contrast between the facial stimuli and the background (Dzhelyova et al., 2017). As this general stimulation response is mainly driven by low-level visual features, it is typically characterized by a medial-occipital topography (Dzhelyova and Rossion, 2014). As this general visual stimulation response is not the focus of this intervention study, we report the results on this base rate response in Appendix Fig. A.1.

2.5 Behavioral facial expression processing

In order to investigate whether potential prosocial OXT effects at the neural level would also be reflected at the behavioral level, we additionally administered the Emotion-matching task (Palermo et al., 2013). This is a computerized facial expression processing task where three faces are shown simultaneously on the screen, and participants have to detect a target face showing a different facial emotion compared to two distractor faces both showing the same expression. All faces display one of the six basic emotions. To ensure that all data was gathered within the assumed 75-minutes window of boosted levels of peripheral OXT (Daughters et al., 2015; Striepens et al., 2013), we used the shorter 65-item version of the task, preceded by four practice trials (for specifics, see Palermo et al., 2013).

2.6 Statistical analyses

We performed repeated measures ANOVAs (‘Afex’ package in R (Singmann et al., 2020)) to assess the modulatory effects of facial expressions and treatment on the participants’ EEG baseline-subtracted amplitudes recorded over the LOT, ROT and MO regions, with *ROI* (LOT, ROT, MO) and *treatment condition* (OXT, PL) as within-subject factors. Considering the previously reported modulatory effect of expression valence on the OXT treatment response (Evans et al., 2014), separate repeated measures ANOVAs were performed for each of the three facial expressions (anger, fear and happiness). Any interaction effect with the factor treatment was also explicitly modelled. Tukey-corrected post-hoc T-tests were performed on the fitted models for all significant effects (‘emmeans’ package (Lenth et al., 2020)). As we were mainly interested in the OXT treatment effect and the modulating influences of person-dependent factors on this treatment effect, we only report these results.

Given that higher levels of autistic traits (Dickter et al., 2018) have been found to relate to socio-emotional face processing, we first explored the effects of person-dependent factors on the baseline (i.e. PL) neural sensitivity for emotional faces, in order to fully comprehend the overall OXT effect. Therefore, additionally, we performed separate ANCOVA analyses including the social subscales of the SRS (*n* = 3) as covariates, first for the placebo session, and subsequently to examine the possible influence of these person-dependent factors on the OXT treatment effect (Bakermans-Kranenburg and van IJzendoorn, 2013; Bartz et al., 2011). In line with our main analysis, and given the specificity of the association between person-dependent factors and the processing of particular emotions (Dickter et al., 2018; Xu et al., 2015), these additional ANCOVAs were performed for each facial expression separately. When modulatory effects of these person-dependent factors were encountered, Pearson correlation coefficients were calculated to visualize the significant relations. We quantified the individual OXT treatment effects for the separate facial expressions by subtracting the EEG amplitudes recorded during the PL session from the EEG amplitudes recorded during the OXT session (i.e. $EEG_{OXT} – EEG_{PL}$).

In keeping with the previous analyses, we also performed repeated measures ANOVAs on the behavioral measures of the orthogonal fixation cross color chance detection task and the Emotion-matching task. For the orthogonal task, within-subject factors were *expression* (anger, fear, happiness) and *treatment condition* (OXT, PL). For the Emotion-matching task, the repeated measures ANOVA only included *treatment condition* as within-subject factor.

Since half of the participants received OXT during their first session, while the other half started with the PL condition, we performed secondary analyses accounting for potential effects of ‘session order’, by adding this factor as a nuisance covariate in all the performed analyses. Overall, the pattern of results was qualitatively similar to the main analyses, confirming no modulatory effect of the factor ‘session order’ on the reported effects.

We applied a Greenhouse-Geisser correction for the degrees of freedom for all repeated measures ANOVAs whenever the assumption of sphericity was violated.

3. Results

3.1 Reported side effects

We monitored potential side effects related to the OXT treatment. As can be observed in Appendix Table A.1, side effects were only minimal, non-treatment specific (cf. insignificant Pearson Chi-square tests), and were possibly due to EEG administration with a tight head cap and fixating on a screen for a prolonged period (e.g. headache reported in 7 OXT and 8 PL participants).

3.2 Expression-discrimination responses

All three expressions elicited clear expression-discrimination responses at the oddball frequency and its harmonics (Fig.2), mostly centered over lateral occipito-temporal sites (Fig. 3).

3.2.1 Estimated reliability and power analysis

A power analysis was performed to calculate the power to detect true differences. The highly reliable measurements (with between-session correlations of $r = .57$, $r = .70$ and $r = .74$ for anger, fear and happiness, respectively; all $p < .001$) included in this repeated-measures design substantially enhanced the power of this study. Based on the average correlation ($r = .67$), a power analysis with G*Power 3 (Faul et al., 2007) revealed a power of .91 to detect group differences, even for a small effect size (0.25), indicating that our study design yielded adequate power.

3.2.2 Neural expression discrimination

No significant main effect of treatment was revealed ($F(1,30)_{\text{Anger}} = 1.07$, $F(1,30)_{\text{Fear}} = 1.51$, $F(1,30)_{\text{Happiness}} = 1.19$; all $p > .23$) – indicating no overall effect of OXT on the neural sensitivity towards different facial expressions (see Fig.3) – nor any significant interaction effect between treatment condition and ROI ($F(2,60)_{\text{Anger}} = 1.95$, $F(2,60)_{\text{Fear}} = 1.76$, $F(2,60)_{\text{Happiness}} = 0.28$; all $p > .15$).

As expected, no treatment effects nor any interactions with treatment were observed for the general visual base rate response (i.e. 6 Hz) for any of the three facial expressions (all $p > .22$, see Appendix Fig A.1).

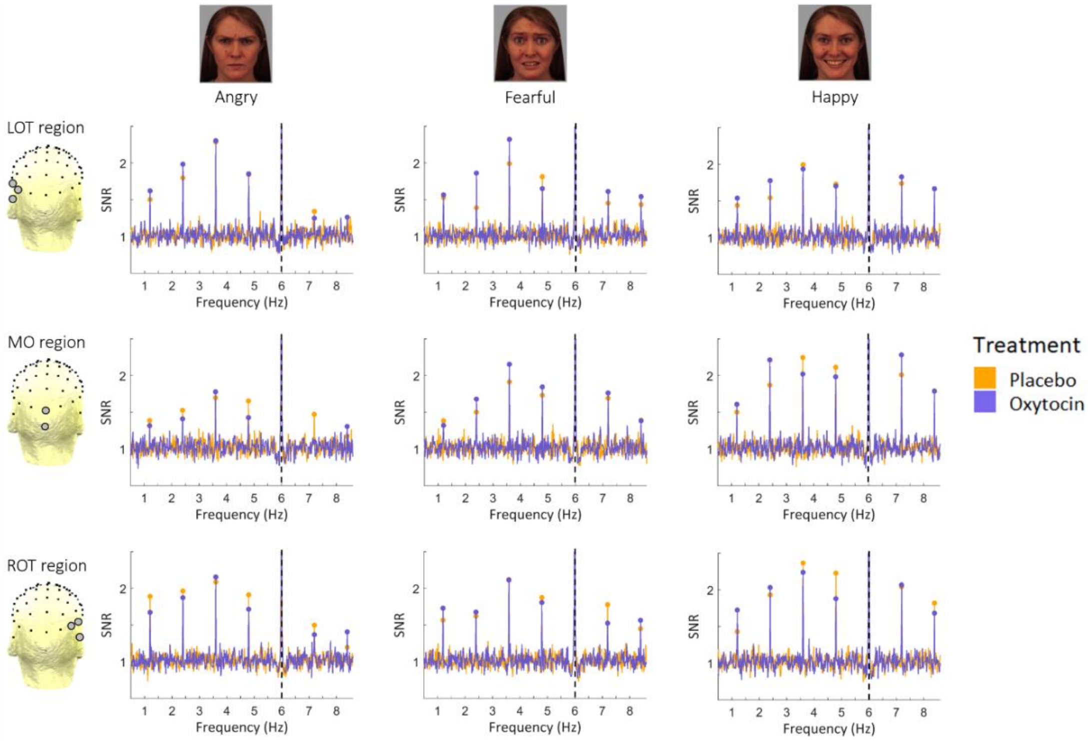

Figure 2. SNR spectra visualizing the expression-discrimination responses. ***Left****: Scalp distribution of the expression discrimination responses, averaged across all three facial emotions and both treatment conditions. The three most leftward and three most rightward open circles constitute left and right occipito-temporal (LOT and ROT) regions, respectively. The two central open circles constitute the medial-occipital (MO) region.* ***Right****: SNR spectra visualizing the expression-discrimination responses, recorded over the LOT (upper row), MO (middle row) and ROT (lower row) regions, for each of the expressions and both treatment conditions. The significant first seven harmonics (until 8.4 Hz) are displayed; the dashed line indicates the 6 Hz base rate response.*

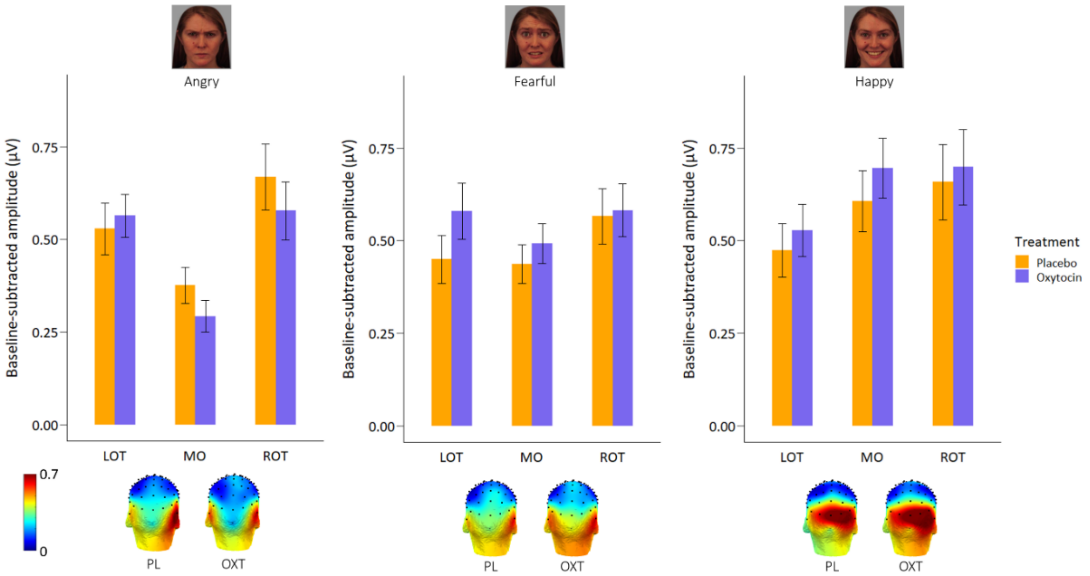

Figure 3. *Expression-discrimination responses. Scalp topographies and bar graphs of the summed baseline-subtracted amplitudes evoked during both treatment sessions, displaying the mean expression-discrimination responses for each of the three ROIs and for each facial expression. Error bars reflect standard errors of the mean.*

3.2.3 Modulatory effects of person-dependent factors on neural expression-discrimination

PL condition. To investigate the influence of individual differences in social skills on the participants' neural sensitivity for specific facial expressions, subsequent ANCOVAs were performed on the brain responses obtained during the PL condition. These additional analyses revealed a significant main effect of the SRS subscale 'Social Awareness' on brain responses while processing angry faces ($F(1,29) = 5.91$, $p = .02$), indicating that the EEG responses towards angry faces are modulated by the participant's ability to pick up on social cues. More specifically, individuals reporting more difficulties on the Social Awareness subscale showed higher EEG amplitudes in the PL condition when processing angry faces ($R = 0.41$, $p = .02$; Fig. 4A), as compared to individuals reporting less social awareness problems. No significant association between the SRS social awareness subscale and neural sensitivity towards fearful ($p = .44$) or happy ($p = .94$) facial expressions was revealed, neither were there any other significant influences of any of the other social subscales of the SRS (all $p > .29$) on the EEG responsivity during the PL condition.

OXT treatment effect. Considering these modulatory effects of social awareness on the neural responses recorded in the PL session, we further examined the possibility of a modulatory impact of this same person-dependent factor on the OXT-treatment response (OT-PL change score). Here, the ANCOVA with within-subject factor *ROI* and *social awareness* as continuous regressor again demonstrated a significant influence of this person-dependent factor on the neural sensitivity for angry faces ($F(1,29) = 4.63$, $p = .04$). As can be observed in Fig. 4B, a more pronounced oxytocinergic treatment effect was found in those individuals who reported more social difficulties ($R = -0.37$, $p = .04$): their high neural sensitivity for angry faces (cfr. EEG responses during PL condition) was attenuated after OXT administration. Treatment effects for processing fear and/or happiness were not significantly modulated by this person-dependent factor (all $p > .39$). Note that the significant ANCOVA results would not survive strict corrections for multiple comparisons. Hence, results need to be interpreted with caution.

Further inclusion of the other social subscales of the SRS revealed no significant influences of these person-dependent factors on the oxytocinergic response (all $p > .21$).

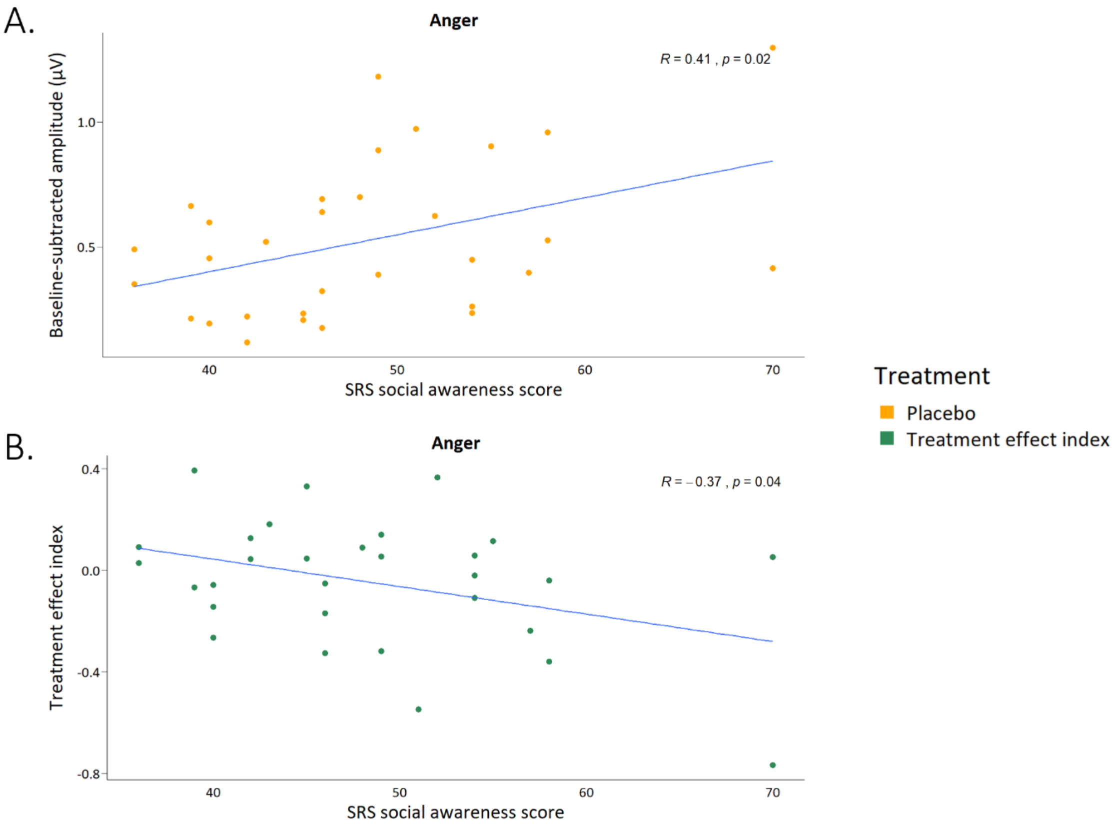

*Figure 4. Visualizing the modulatory effect of social awareness on the neural sensitivity for angry faces. Data points are averaged across all three ROIs for each participant. **(A)** Participants with more reported problems on the SRS subscale Social Awareness showed higher neural sensitivity for angry faces. **(B)** The OXT treatment effect was larger in participants who reported more social awareness problems, in the sense that a single dose of OXT attenuated their bias for angry faces (as encountered in the PL condition). Note the difference in y-axis scaling.*

Altogether, these findings indicate that individual differences in socio-cognitive skills modulate both the neural sensitivity for specific facial expressions, and the OXT treatment effect on this neural sensitivity. More specifically, especially for angry faces, participants who reported more problems on the Social Awareness subscale of the SRS demonstrated higher EEG amplitudes as compared to the other participants in the PL condition. Accordingly, this same subgroup also showed the largest OXT induced attenuation of neural responsivity to this negative expression.

3.3 Behavioral measures: Orthogonal task and explicit facial emotion processing

Results of the repeated measures ANOVA revealed equal performances during the PL and OXT sessions on the fixation cross color change detection task, both in terms of accuracy (M_{PL} = 95%, SD_{PL} = 0.05; M_{OXT} = 95%, SD_{OXT} = 0.06; $F(1,30) = 0.0032$, $p = .95$) as well as in terms of reaction times (M_{PL} = 0.43 s, SD_{PL} = 0.05; M_{OXT} = 0.43 s, SD_{OXT} = 0.04; $F(1,30)$ =

1.06, *p* = .31). These results clearly indicate that the participants were equally attentive to the screen within each treatment session.

In addition, the repeated measures ANOVA investigating the participants' performances on the Emotion-matching task also revealed equal accuracy (M_{PL} = 75%, SD_{PL} = 0.07; M_{OXT} = 74%, SD_{OXT} = 0.10; *F*(1,30) = 0.12, *p* = .73) and equal reaction times (M_{PL} = 4.11 s, SD_{PL} = 1.31; M_{OXT} = 4.03 s, SD_{OXT} = 1.16; *F*(1,30) = 0.72, *p* = .40). Also no significant influence was revealed of any of the person-dependent factors on the performance during the PL condition or on the treatment effect (all *p* > .22). Hence, these results suggest that neither OXT treatment, nor person-dependent factors have a modulatory effect on explicit facial expression processing.

4. Discussion

In the current randomized, double-blind, cross-over, placebo-controlled study, we applied frequency-tagging EEG to investigate the facilitating effects of a single dose of OXT on the automatic and implicit neural sensitivity of 31 healthy adult men to brief changes in facial expression.

Whereas we did not find an overall OXT treatment effect, OXT treatment responses were modulated depending on person-dependent factors (level of social proficiency) and contextual factors (valence of facial expressions), suggesting that in individuals with more difficulties in the social domain (lower self-reported social awareness), OXT attenuated the neural bias towards angry facial expressions. Behavioral tasks assessing emotion processing performance revealed no overall or modulated treatment effect depending on person-dependent factors.

Similar to what has been demonstrated before with comparable frequency-tagging EEG paradigms (Dzhelyova et al., 2019), the neural expression-discrimination responses obtained in our study showed a high test-retest reliability. As can be expected based on the influences of person-dependent factors, however, the test-retest reliability dropped for the processing of angry faces due to the differential effect of OXT for a certain subsample of participants.

4.1 OXT-related modulations of the neural sensitivity to angry faces depends on person-dependent-factors

Examination of the modulatory effect of person-dependent factors on facial expression processing during the placebo condition revealed an influence on the neural discrimination of angry faces. Particularly, participants who reported more difficulties to pick up on social cues (i.e. social awareness) showed higher EEG amplitudes during the PL session while processing angry faces, as compared to participants with less social awareness problems. As higher scores on the social SRS subscales indicate more social difficulties related to autism spectrum disorder (and thus, higher autistic traits), our findings suggest that a higher prevalence of autistic traits in healthy individuals is related to an enhanced neural sensitivity to negative facial emotions. These findings are largely in line with previous studies showing that neurotypical individuals with high levels of autistic traits demonstrate preferential attention (Ribeiro and Fearon, 2010) or increased neural reactivity (Cooper et al., 2013) to negative emotional faces, as well as reduced neural reactivity to positive facial expressions (Cooper et al., 2013; Gayle et al., 2012).

Notably, in the current study, we revealed a significant influence of social awareness on the OXT treatment effect, indicating a more pronounced treatment effect in participants who reported more social difficulties. In other words, these participants – who showed a higher neural sensitivity to angry faces during the placebo session – displayed an attenuated bias in neural sensitivity to this facial expression after a single dose of intranasal OXT as compared to participants with less social difficulties. These results are consistent with previous reports of OXT administration attenuating the attentional bias for negative emotions (e.g. angry faces; which we found at baseline) (Ellenbogen, 2018; Kim et al., 2014).

Further, the modulation by person-dependent factors is supportive of previous reports highlighting the relevance of inter-individual differences in personal characteristics on OXT treatment responses. Previously, several studies have reported differences in social skills or attachment style to modulate the effect of a single dose of OXT (Bakermans-Kranenburg and Van IJzendoorn, 2013; Bartz et al., 2010; Prinsen et al., 2018), with more beneficial effects in individuals who are less socially adapted or less securely attached.

4.2 No general enhancement of emotional salience, but an attenuation of social withdrawal tendencies

In general, the finding of attenuating instead of enhancing effects of OXT on neural sensitivity towards angry facial expressions, argues against a strong account of the social salience hypothesis of OXT (Shamay-Tsoory and Abu-Akel, 2016). Although this framework takes the modulatory influences of personal characteristics on OXT treatment effects into account, it posits that OXT uniformly increases the salience of social stimuli, irrespective of their valence. This was not the case in our study. Instead, our pattern of results points towards a modulation of OXT treatment responses depending on person-dependent factors (level of social proficiency) and contextual factors (valence of facial expressions), suggesting that in certain subpopulations (i.e. individuals characterized by socio-cognitive impairments), OXT can attenuate the neural sensitivity towards negative facial expressions.

Our findings align more with the social approach/withdrawal hypothesis (Kemp and Guastella, 2011), stating that OXT enhances social approach-related behavior and diminishes social withdrawal. At a neural level, this is reflected in increased activation when processing positive facial expressions and reduced responses when processing negative facial expressions. Pertaining to our results and considering that angry faces with direct gaze signal threat directed at the observer (Sander et al., 2007), a single dose of OXT might alleviate the automatic threat-related processing (Ellenbogen, 2018) – and thus, in extension, the withdrawal-type behaviors that are elicited (Kemp and Guastella, 2011) – when perceiving angry faces, to promote approach behavior, especially in individuals with more socio-communicative difficulties.

The absence of a significant influence of OXT on the neural sensitivity to fearful faces might suggest that the balance between approach- and withdrawal-related behavior may have been adequate already when processing this facial expression. Furthermore, we neither observed an oxytocinergic effect for positive facial expressions, as may have been reflected in enhanced neural activity to happy faces. However, as the oxytocinergic effects in response to positive and negative facial expressions are thought to be largely independent of each other (Ellenbogen, 2018), it is not too surprising that we did not observe larger neural responses to happy faces in addition to the attenuated neural response to angry faces.

4.3 No modulation of behavioral emotion matching performance in healthy individuals

In addition, we found no improvement of behavioral facial emotion processing after OXT administration. However, it should be noted that the participants included in our study were healthy adults with moderate to high social processing skills (i.e., social SRS scores ranging between 37 and 66) and adequate baseline emotion processing abilities (Palermo et al., 2013; Supplementary results S1). Although OXT has improved sociality in neurotypicals as well, larger effects have been reported in patient populations. Accordingly, the possibility cannot be ruled out that the lack of OXT treatment effects on the behavioral emotion processing task might reflect ceiling performance, allowing no further behavioral improvement (Bartz et al., 2011). Indeed, the current observation that OXT attenuated neural sensitivity towards angry expressions, especially in participants with low social sensitivity, suggests that treatment effects may become more apparent or enlarged in patient populations that have more severe social impairments, such as individuals with autism spectrum disorder (a notion that has been suggested before by Wang et al., 2017).

5. Conclusion

We applied frequency-tagging EEG to investigate the effects of a single dose of OXT on the automatic and implicit neural sensitivity for positive and negative facial expressions. Although we did not find an overall effect of OXT on facial emotion processing, a modulation of the OXT treatment effect was found depending on person- and context-dependent factors, indicating that in participants with low self-reported social awareness, a single dose of OXT administration was able to attenuate their augmented sensitivity to angry faces.

6. Supplementary materials

Table A.1. Frequency of the reported side effects and their severity.

Side effects	Mild		Moderate		Severe		Total			
	PL	OXT	PL	OXT	PL	OXT	PL	OXT	Chi-square	*p*-value
Headache	6	6	1	1	1	0	8	7	0.07	0.80
Drowsiness	8	8	2	0	1	2	11	10	0.05	0.83
Dizziness	3	2	0	0	0	0	3	2	0.2	0.65
Fainting	0	0	0	0	0	0	0	0	0.00	1.00
Changes in heart rate or palpitations	0	0	0	0	0	0	0	0	0.00	1.00
Shortness of breath	0	0	0	0	0	0	0	0	0.00	1.00
Fever	0	0	0	0	0	0	0	0	0.00	1.00
Sore throat	0	0	0	0	0	0	0	0	0.00	1.00
Dry mouth / throat	10	10	0	1	0	1	10	12	0.18	0.67
Hoarseness	0	0	0	0	0	0	0	0	0.00	1.00
Coughing	2	2	0	1	0	0	3	2	0.2	0.65
Coughing up phlegm	0	0	0	1	0	0	0	1	1.00	0.32
Congested nose	2	2	0	0	0	0	2	2	0.00	1.00
Sneezing	1	0	0	0	0	0	1	0	1.00	0.32
Runny nose	0	3	1	1	0	0	1	4	1.8	0.18
Watery eyes	6	4	2	2	0	0	8	6	0.29	0.59
Nausea and/or vomiting	0	0	0	0	0	0	0	0	0.00	1.00
Abdominal or stomach pain	0	0	0	0	0	0	0	0	0.00	1.00
Changes in perception of the tongue	0	0	0	0	0	0	0	0	0.00	1.00
Burning sensation in nose and/or ears	0	0	0	0	0	0	0	0	0.00	1.00
Muscle pain/cramps	0	1	0	0	0	0	0	1	1.00	0.32
Skin rash	0	0	0	0	0	0	0	0	0.00	1.00
Blurred vision	2	2	1	2	0	0	3	4	0.14	0.71
Sensitive to fragrances	0	0	0	0	0	0	0	0	0.00	1.00
Transpiration	2	2	1	2	0	0	3	4	0.14	0.71

Participants reported and rated (mild, moderate, severe) the side effects they experienced throughout each session. The absence of significant group differences (via Pearson Chi-square test) indicated only minimal, non-treatment specific side effects.

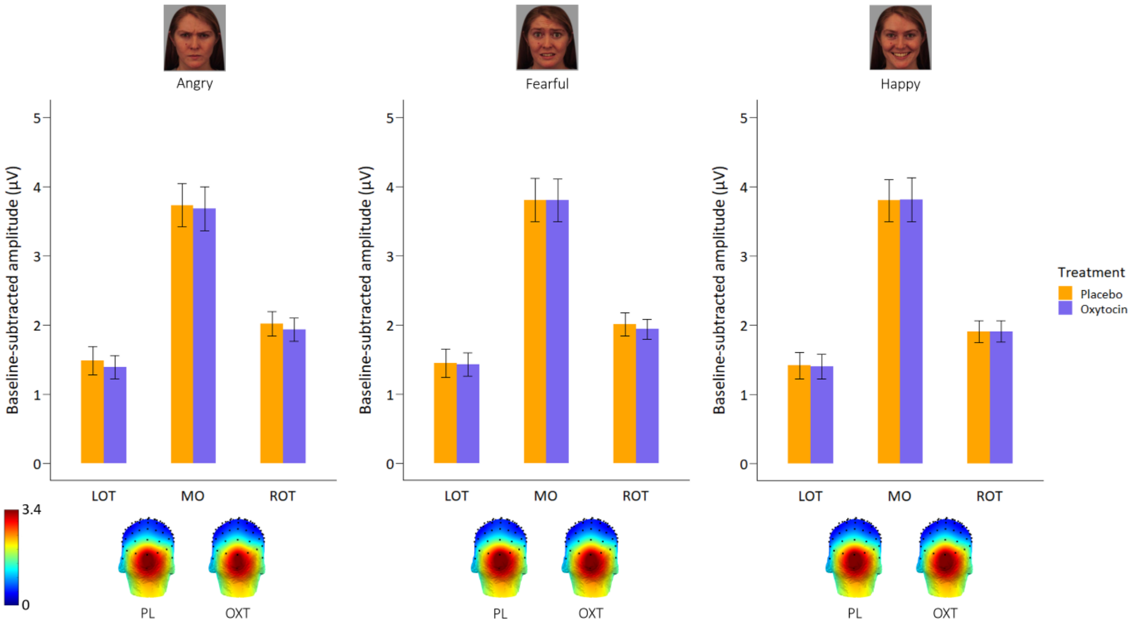

Figure A.1. General visual base rate responses. Similar general visual responses to faces, mostly recorded over medial-occipital sites, irrespective of the treatment condition or facial expression.

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General Discussion

1. Summary of the main findings

The overall aim of the present dissertation was to provide more insight in the automatic facial emotion processing mechanisms in a typical and an atypical population using a series of implicit and explicit measures. Five studies, which were reported in the previous chapters and are summarized below, were conducted to achieve the doctoral project's objectives.

Part I. Back to basics

In our first study **(chapter 1)**, we applied an FPVS sweep oddball paradigm in combination with frequency-tagging EEG to pinpoint the threshold of optimal SF information for the rapid detection of fearful facial expressions. By progressively adding extra SF information to images containing either only very low or very high SFs, we systematically swept through an entire SF range without decomposing the images into discrete SF bands. 30 healthy, young adult participants participated in this study. Results indicated that faces require at least SF information higher than 5.93 cpi to implicitly differentiate fearful from neutral faces. However, exclusive HSF faces, even in a restricted SF range between 94.82 and 189.63 cpi already carry the critical information to extract the emotional expression of the faces. We ensured that we were effectively quantifying sensitivity for fearful expressions and not merely sensitivity to subtle featural perceptual changes by (i) continuously changing the stimulus size, and (ii) additionally presenting the images upside-down. The presence of a significant inversion effect guaranteed that the neural detection of the fearful faces was not merely driven by sensitivity to low-level perceptual changes. In line with the flexible usage theory (Morrison & Schyns, 2001; Ruiz-Soler & Beltran, 2006) we found that the diagnostic SF information differed slightly dependent whether fearful faces had to be discriminated implicitly versus explicitly: a slightly broader SF range was involved in explicit versus implicit fear detection.

Part II. (A)typicalities in facial expression processing

In **chapter 2,** we investigated the neural sensitivity of 23 school-aged boys with ASD and 23 matched TD boys to rapidly and implicitly discriminate fearful faces, again using FPVS in combination with frequency-tagging EEG. Here, we presented the faces either upright or inverted, to assess possible differences in perceptual strategies. In addition, by positioning the fixation cross either on the nasion or on the mouth of the faces, we explored whether the detection of a fearful face is modulated by directing the participants' attention to either of those regions. We found that both groups equally displayed the face inversion effect, suggesting that they both applied a holistic facial expression approach, additionally supported by an effective feature-based approach, as indicated by the activation of the medial-occipital brain region. In addition, the higher neural responses in both groups when the participants' attention was directed to the mouth, indicates that the mouth is the most informative region for boys with ASD and TD boys to implicitly detect fearful faces. However, while both groups thus displayed a similar perceptual strategy and relied on the same facial information, boys with ASD showed reduced neural responses to rapid changes in expression, as compared to TDs, which possibly contributes to the emotion processing difficulties. At an individual level, the distinct fear discrimination responses allowed to predict clinical status with an 83% accuracy. This study is published in *Journal of Autism and Developmental Disorders* (Van der Donck et al., 2019).

In a subsequent study with the same participants **(chapter 3)**, we examined whether the lower neural sensitivity in boys with ASD was specific for fear, or whether it would generalize to other expressions as well. Therefore, we included the additional emotions anger, happiness and sadness in the FPVS oddball paradigm. Our results suggested a rather-emotion specific reduced neural sensitivity, as only fearful and angry faces elicited significantly lower brain responses in boys with ASD. These significant amplitude differences allowed 87% correct classification of participants with ASD. Sadness and happiness evoked similar neural responses in both groups. However, given the significantly lower detection responses for sad faces in the TD group, possible floor effects may have masked potential group differences. Furthermore, intact detection of rapidly presented happy faces in boys with ASD should not be surprising, as it is the emotion that is recognized the easiest and earliest (De Sonneville et al., 2002; Herba & Phillips, 2004; Mancini et al., 2013), needing only minimal signals (Luyster et al., 2017; Rodger et al., 2015). Additionally, if responses had been determined by stimulus properties, rather than the emotional content of the faces, the pattern of neural expression-discrimination responses would mirror the pattern of stimulus-based differences for each of these emotions relative to the neutral baseline. However, the fine-grained evaluation of the stimulus properties demonstrated that this was not the case, especially for TD boys. Yet, in the ASD group, the brain responses seemed to be more in line with the intrinsic stimulus characteristics, which might suggest a stronger reliance on the physical stimulus features instead of the emotional meaning of the stimulus. This study was published in *Journal of Child Psychology and Psychiatry* (Van der Donck et al., 2020).

To expand our understanding of the automatic emotion processing mechanisms in boys with and without ASD beyond the neural level, we examined their spontaneous facial mimicry and eye gaze patterns during an explicit emotion recognition task **(chapter 4)**. When labelling facial expressions, participants of both groups employed similar eye gaze strategies. Yet, boys with ASD varied their scanning patterns less in relation to the emotional content of the faces as compared to TD boys. Moreover, modelling of the individual temporal scanning dynamics and the larger saccadic amplitudes in TD boys suggested a less exploratory face processing strategy in boys with ASD. However, given their equal behavioural emotion recognition performances, their slightly more persistent visual scanning behaviour did not impede the processing of emotional information. Regarding the facial mimicry results, we found similar facial responses to emotional faces in boys with and without ASD. However, based on the very low intensity values of all expressions other than neutral, we concluded that the Emotion Recognition Task (Montagne et al., 2007) did not elicit clear facial responses, and might thus not have been suited to investigate spontaneous facial mimicry.

Part III. To sniff or not to sniff?

In the last chapter of this doctoral dissertation **(chapter 5)**, we explored the effect of a single dose of oxytocin (24 IU) on the neural sensitivity of healthy young adults to different facial expressions in a randomized, double-blind, within-subjects, cross-over, placebo-controlled study. Overall, we found no effect of oxytocin on the neural sensitivity to specific facial emotions, nor on the behavioural emotion processing. However, the oxytocin effect was modulated by person-dependent factors: the higher neural sensitivity in individuals reporting less social awareness for angry faces encountered at baseline was attenuated after oxytocin administration.

2. Facial emotion processing in typically and atypically developing children

2.1 At a neural level

The implicit expression-discrimination responses evoked during the EEG paradigms demonstrated a reduced sensitivity in boys with ASD for angry and fearful (both in a single identity and across multiple identities) faces (Van der Donck, 2020, 2019). A threat bias, which has often been reported in TD individuals and has been related to evolutionary survival strategies (Hedger et al., 2016; Lyyra et al., 2014), might have selectively boosted the oddball responses for angry and fearful faces in the TD group (R. C. Leung et al., 2019). Although a threat-superiority effect (i.e. the rapid detection of threatening faces) also has been observed in children with ASD (May et al., 2016; Rosset et al., 2011), the brain responses of the boys included in our study did not point in that direction. Neither did these results indicate an overall lower sensitivity to negative emotions in boys with ASD (Ashwin et al., 2006), given the equal neural discrimination responses for sad faces. However, considering that sad faces elicited significantly lower responses in the TD group as compared to the other emotions, possibly because sadness does not display very prominent, emotion-characteristic facial features (Calvo & Nummenmaa, 2008) and has been found to be a difficult emotion to distinguish from neutral expressions (Gao & Maurer, 2010), floor effects may have masked potential group differences. In addition, although recent reviews reported differences in neural responses to happy faces (Black et al., 2017; Monteiro et al., 2017), happiness also evoked similar neural activations in both groups. The distinct smile may be easily detectable, even when attention is oriented towards the eye region using a fixation cross.

Given the typical age-related improvement of facial expression processing (De Sonneville, 2002; Herba et al., 2006; Luyster, 2017; Mancini, 2013) and the profound maturation of these abilities during adolescence (Blakemore, 2008; Nelson et al., 2005), we can assume that specialization of the emotion processing abilities was still ongoing in the children included in our study. Hence, even before reaching fully matured automatic emotion processing in the TD group, differences in neural sensitivity for specific emotions could already be identified in boys with ASD. Considering that ASD is a neurodevelopmental disorder (American Psychiatric Association, 2014), one could argue that the fear and anger processing abilities in boys with ASD follow a delayed trajectory, which might explain the neural results. However, the behavioural recognition performances contradict this: without displaying any response bias, anger was one of the emotions most often labelled correctly in both participant groups, whereas both TD boys and boys with ASD made most labelling mistakes for fear.

The progressive tuning of the neural system involved in (expressive) face processing (Cohen Kadosh & Johnson, 2007; Leppänen & Nelson, 2009) is enhanced by social experiences (Greenough et al., 2008), hence, deprivation of social interaction might hamper further specialization. The social motivation theory (Chevallier et al., 2012) states that individuals with ASD show a reduced tendency to orient to social stimuli and to engage in social interactions, as it is less rewarding for them in comparison to TDs (Clements et al., 2018). As many individuals with ASD tend to participate in fewer social interactions in comparison to TD individuals from a young age on (Lord & Magill-Evans, 1995), they might not acquire the emotional face processing experiences necessary for typical maturity of these abilities. However, this does not explain the overall neural pattern displayed in the participants with ASD: if the social motivation theory, and, thus, the lack of social experiences, would account for the neural responses, we would expect an overall lower sensitivity and not only for two specific emotions. Unless, of course, boys with ASD are significantly more familiar with happy versus angry and sad faces. Combined with the potential floor effects encountered in the TD group for sad faces (as explained in the previous section), this might then provide an explanation.

Disturbances in the experience-driven development of facial emotion processing might also lead to reduced interconnectedness between different brain regions (Müller et al., 2011). In TD individuals, increased levels of threat have been found to elicit increased activity in the amygdala, as well as in the fusiform gyrus and the STS (Ashwin et al., 2007), clearly indicating interconnectedness. This might explain the higher occipito-temporal brain responses found in the TD participants when implicitly processing fearful faces.

According to the theory of underconnectivity (Just et al., 2012) and the Amygdala Theory of Autism (Baron-Cohen et al., 2000), hypo-activation in the amygdala and atypicalities in the connections between brain regions involved in perceiving and assessing socio-emotional information might account for the social deficits characteristic for ASD. Hypo-activation of the amygdala has, indeed, frequently been found (for a meta-analysis, see (Aoki et al., 2015)), especially when processing fearful faces (Ashwin, 2007; Kim et al., 2015). Hence, given the interconnectedness of the amygdala and the fusiform gyrus and STS (among others), hypo-activation of the amygdala in response to these expressions, a reduced functional connectivity between the social brain areas and the amygdala, or a combination of both could possibly explain the reduced occipito-temporal activation in boys with ASD when processing angry and fearful faces. However, these are mere speculations, as EEG does not allow to (directly) investigate the activity in subcortical areas or the connection between brain regions.

2.2 Rule-based behavioural compensatory strategy in boys with ASD

Interestingly, notwithstanding the reduced neural sensitivity for fearful and angry faces, participants with ASD showed equal behavioural emotion recognition performances as TD controls. Intact facial emotion recognition has been observed in many previous studies (Lacroix et al., 2014; D. Leung et al., 2013; Tracy et al., 2011). However, it might reflect the use of compensatory mechanisms (Harms et al., 2010), rather than genuine equal emotion processing. Our findings seem to align with this notion, especially considering the lower neural sensitivity to angry and fearful faces and the absence of reduced behavioural recognition of these emotions.

During the Emotion Recognition Task (Kessels et al., 2014; Montagne, 2007), the emotion labels are presented on the left side of the screen. Possibly, seeing these labels might have facilitated the facial expression recognition. Moreover, individuals with ASD have been found to employ higher-order heuristics based on changes in specific facial features (i.e. rule-based) to perceive and interpret facial expressions, whereas TD individuals recognize a facial emotion by automatically matching it to a prototypical representation (Rutherford & McIntosh, 2007; Walsh et al., 2014). Hence, given the similar behavioural outcomes in both groups, the rule-based compensatory strategy applied in the ASD group seems to have allowed accurate facial emotion recognition, despite their lower neural sensitivity to a subset of these facial expressions. As the design of our EEG paradigm, with the neutral faces acting as forward and backward masks for the expressive faces, as well as its rapid presentation (i.e. implying a short presentation duration), effectively prevented the use of these explicit compensatory mechanisms (Frank et al., 2018), actual differences in automatic emotion processing were revealed.

The use of rule-based compensatory mechanisms might also explain why we did find significant differences in the emotion-matching performances of boys with and without ASD in addition to the equal emotion recognition. In the Emotion-matching task, target faces are paired with maximally confusable distractor emotions, involving similar low-level features (Palermo et al., 2013). Hence, the rule-based decoding of facial expressions to recognize emotions (i.e. relying on the separate facial features instead of the configuration of the facial expressions) could not be applied when matching emotional faces with similar low-level facial cues to detect the odd-one out.

2.3 Extracting emotional information

2.3.1 Combined holistic and feature-based perceptual strategy in ASD and TD

Relying on the separate facial cues to process facial emotions suggests a more local, feature-based perceptual processing style in individuals with ASD (Behrmann et al., 2006; Tanaka & Farah, 1993). However, our results provide no conclusive evidence to support this. First, we found a face-inversion effect in both groups when implicitly detecting fearful faces, indicating that boys with and without ASD generally apply a holistic perceptual emotional face processing style. The concurrent activation in the medial-occipital brain region – involved in more low-level visual processing (Dzhelyova & Rossion, 2014; Liu-Shuang et al., 2014) – when detecting fearful faces in a single identity, however, signifies the additional support of an effective feature-based approach in both boys with ASD and TD boys. In spite of the continuous size changes of the stimuli, the open mouth might have facilitated fear detection. Indeed, facial expression processing – and in particular fear detection (Bombari et al., 2013) – can be more strongly determined by the processing of salient facial features, such as the open mouth, as opposed to the configural relationship between those features (Sweeny et al., 2013). However, further evidence for the holistic approach in both groups was provided by the presence of clear emotion-discrimination responses across continuously changing identities in almost all participants ((Van der Donck, 2020), table S1), as this evidently required processing the faces as a whole (gestalt). Together, these findings indicate that school-aged boys can process emotional faces holistically, yet, prefer to apply a feature-based approach if possible.

Still, the brain responses of boys with ASD were more in line with the intrinsic stimulus characteristics as compared to TD boys, yet, without significant amplitude differences between the emotions. This might suggest a stronger reliance on the physical stimulus features, instead of the emotional content of the faces, which resonates with the enhanced perceptual functioning (Mottron et al., 2006) and the weak central coherence (Happé & Frith, 2006) accounts. These accounts propose that perceptual processing in ASD is more feature-based and locally oriented, whereas in TDs it is more globally driven and oriented towards integrating information into a meaningful whole (gestalt).

2.3.2 Less exploratory gaze behaviour in boys with ASD

This slightly higher reliance on separate facial cues – and, thus, in extension, the slightly lower dependence on the emotional meaning of the stimuli – converges with the eye tracking data obtained during explicit emotion recognition. Overall, boys with and without ASD seemed to employ similar perceptual eye gaze strategies during emotion recognition. Yet, small underlying differences were revealed.

Although participants of both groups displayed an equal number of fixations and equal fixation durations, we found higher saccadic amplitudes in TD boys, as compared to boys with ASD. Saccadic amplitudes can be interpreted as a measure of visual exploration (Vabalas & Freeth, 2016), hence, indicating that boys with ASD tend to fixate on locations that are near to the previous one, whereas TD boys shift their gaze across wider distances. In combination with the modelling of the temporal scanning dynamics, these saccadic amplitudes suggest a slightly less exploratory and a slightly more persistent processing strategy in boys with ASD. The lower saccadic amplitudes recorded in the ASD group may encompass a more detail-focused visual exploration strategy in local areas (Heaton & Freeth, 2016; Vabalas, 2016), which aligns with the slightly higher reliance on individual facial features during implicit facial emotion processing and possibly aids the rule-based emotion recognition (i.e. compensatory mechanism). In addition, TD boys fixated more on the eyes than the nose and mouth when viewing angry and sad faces; boys with ASD did not display such differentiated gaze behaviour. Typically, individuals do indeed tend to vary their scanning patterns in function of the emotional content of the faces (Beaudry et al., 2014) and focus more on the eyes when processing negative facial expressions, as they seem to convey the most informative facial information (Eisenbarth & Alpers, 2011; Guarnera et al., 2017; Wegrzyn et al., 2017). Although adapted scanning patterns have also been reported in individuals with ASD (de Wit et al., 2008), we did not find similar results in our ASD group.

Irrespective of whether or not this more locally focused gaze behaviour in boys with ASD is part of the rule-based compensatory mechanism, their more persistent and less differentiated scanning patterns did not imply less efficient facial information processing, given their equal behavioural recognition performances with similar timings.

2.3.3 No eye avoidance in boys with ASD

Less varied face scanning patterns in function of the expressed emotion could possibly result in reduced emotion recognition, considering that different face regions display information necessary to decode specific emotions. The mouth region has been identified as the most informative face area for the recognition of positive expressions (Eisenbarth, 2011; Wegrzyn, 2017). Indeed, the recognition of happiness, for example, relies mainly on information from the mouth (Beaudry, 2014; Bombari, 2013; Eisenbarth, 2011). On the other hand, the eyes are found to be the most important for the recognition of negative expressions, such as sadness and anger (Eisenbarth, 2011; Guarnera, 2017), or fear (Bombari, 2013). However, other studies have emphasized the equal importance of both the eyes and mouth for fear processing (Eisenbarth, 2011), or have even highlighted the necessity of their configural combination (Beaudry, 2014).

According to the Eye Avoidance Hypothesis (Tanaka & Sung, 2016), individuals with ASD avoid looking at the eye region as an adaptive strategy, because the eyes are perceived as a socially threatening stimulus. In addition, reduced eye contact is one of the clinical criteria of ASD (American Psychiatric Association, 2014). However, the empirical evidence that individuals with ASD focus less on the eyes and more on the mouth is not unequivocal (Bal et al., 2010; Black, 2017; Guillon et al., 2014). Nevertheless, if participants with ASD fail to inspect the most informative facial cue (e.g. the eyes), their facial emotion processing would be impaired (Ellison & Massaro, 1997).

Our results, however, indicate that both boys with and without ASD are capable of extracting the critical emotional information from the faces to reach accurate facial expression processing. For example, during one of the implicit frequency-tagging EEG paradigms (Van der Donck, 2019), we directed the participants' attention to either the eyes or the mouth of the stimuli via a fixation cross. Here, we found that, apparently, for both groups of children, the mouth was a more salient cue to rapidly detect fearful faces than the eyes. The mouth has indeed been suggested to be the most informative area for expression processing (Blais et al., 2012). When presented opened, it might enhance early automatic attention (Langeslag et al., 2018), probably because of the contrast of white teeth against a darker mouth opening and lips (DaSilva et al., 2016). However, this does not imply that the eye region was redundant, given that attending to the eyes also evoked clear expression-discrimination responses in participants from both groups, even across continuously changing identities (Van der Donck, 2020).

Additionally, the eye tracking data revealed that participants with ASD also clearly focused on the eyes of the expressive faces. Hence, as elaborated in the previous section, boys with ASD are able to attend to the most informative facial cues and extract the critical information for facial expression processing, in spite of their less exploratory face scanning approach.

3. Facial emotion processing in healthy adults

3.1 Extracting emotional information from HSF versus LSF visual input

Findings from previous studies investigating the role of SFs for fearful face processing are highly inconsistent. For example, both a LSF (Holmes et al., 2005; Pourtois et al., 2005; Vlamings et al., 2009) and HSF (Smith & Merlusca, 2014; Stein et al., 2014) bias have been reported for fear processing, as well as the importance of the MSF range (Gao & Maurer, 2011). Our results are in line with a bias for higher SFs (Goren & Wilson, 2006), as automatic discrimination between neutral and fearful faces was impaired for LSF-filtered faces, compared to faces containing medium or higher SFs. Indeed, to extract the critical facial information to rapidly and implicitly detect fearful faces in the stream of neutral faces, healthy adults require the faces to comprise at least SF information higher than 5.93 cpi Still, the amplitude of the fear-discrimination response kept increasing when adding higher SFs, even after reaching the initial detection threshold – i.e. the minimally required SF content to elicit significant brain responses to fearful faces. Perhaps visual encoding is facilitated by a progressive generalization of more accurate visual representations of fearful faces based on the continuous accumulation of relevant higher SFs (Quek et al., 2018).

In addition to the beneficial additive value of adding higher SFs to LSF images, we found that HSFs themselves (even in the restricted range between 94.82 and 189.63 cpi) were sufficient to detect fearful faces. HSFs carry more detailed and richer information (Goffaux et al., 2005), which is apparently the critical information to extract the emotional expression of the faces (McBain et al., 2012; Quek, 2018).

Similar as in our child studies, we found an inversion-effect in healthy adults, indicating that they process the faces holistically, as inversion disrupts their typical processing style and forces them to apply a feature-based approach (Tanaka, 1993). Given that HSF information conveys the detailed facial information and thus allows to process the faces easier when presented upside-down as compared to faces mainly containing LSF information, this inversion-effect was more pronounced for faces containing more LSFs.

The flexible usage theory states that the diagnostic SF information invoked for carrying out particular processes depends on the particular task demands (Morrison, 2001; Oliva & Schyns, 1997; Ruiz-Soler, 2006). Our results seem to support this: fearful faces can be detected based on a subset of SFs (De Cesarei & Codispoti, 2013), yet, this subset differs (slightly) for implicit versus explicit fear detection. More specifically, we found that healthy adult participants required (a little bit) more SF information when explicitly processing fearful faces, as compared to implicitly. This entails that the SF range for explicit fear detection was stretched towards the mid-SF band, which carries both configural and featural information (Watier et al., 2010) and has been identified as optimal for facial expression processing at the behavioural level (Gao, 2011; Plouffe-Demers et al., 2019).

Possibly, to decide with certainty whether fearful faces are really perceived, participants relied on a broader SF range that increased the visibility of the oddball stimuli.

3.2 The effect of intranasal oxytocin on facial emotion processing

OXT functions as a neuromodulator of prosocial behaviour and socio-cognitive processes (MacDonald & MacDonald, 2010; McClung et al., 2018; Viero et al., 2010; Wigton et al., 2015). Although it, generally, has been thought to invariantly improve prosocial behaviour and social cognition, its effect is highly variable and is modulated by person-dependent factors and the social context (Bartz et al., 2011; Evans et al., 2014). For instance, effects of OXT have mainly been observed in those individuals who initially (i.e. before OXT treatment) scored low in terms of social-cognitive competence (Bartz et al., 2010), and high on anxious attachment (Bartz, 2010; Bartz, 2011).

Whereas some studies found an overall improvement of facial expression recognition, irrespective of the valence of the expressions (Guastella et al., 2010; Lischke et al., 2012), others have reported an OXT effect for positive (Di Simplicio et al., 2009; Marsh et al., 2010; Schulze et al., 2011) or negative (Fischer-Shofty et al., 2010) emotions only. Here, we found no effect of OXT on the behavioural emotion processing of healthy adult participants. Some studies showed that the OXT induced improvement was dependent on task difficulty (Domes et al., 2007; Guastella, 2010). Given that we included healthy adult participants who probably already reached ceiling levels for emotion recognition, the task might have been too easy to allow further improvement.

From a social information processing perspective, there are three main potential effects of OXT: (i) facilitating the positive emotion processing, (ii) attenuating the negative emotion processing, and (iii) increasing the social salience in general, irrespective of valence (Bartz, 2011; Churchland & Winkielman, 2012; Ellenbogen, 2018; Shamay-Tsoory & Abu-Akel, 2016). We found no overall effect of OXT on the neural sensitivity to specific facial emotions, implying the absence of supportive evidence for the social salience hypothesis (Shamay-Tsoory, 2016). Instead, we found that a single dose of OXT attenuated the sensitivity for angry faces, which aligns more with the social approach/withdrawal hypothesis (Kemp & Guastella, 2011). This theory posits that OXT enhances social approach-related behaviour and diminishes social withdrawal. Accordingly, the reduced neural response to angry faces may indicate the dampening of withdrawal-type behaviours that were elicited, in favour of approach behaviour. Importantly, this effect was only present in individuals who reported more social problems, confirming, indeed, the variable and person-dependent nature of the OXT treatment effect. Given this person-dependent influence and the fact that OXT seems to mainly exert its effect in individuals with more social difficulties, our findings might provide first indications for effective treatment interventions in enhancing the emotional face processing skills, for example, in individuals with ASD.

4. Methodological considerations

In light of the multiple possible influences on explicit behavioural facial emotion processing, we applied a series of implicit measures to gain more insight in the automatic emotion processing mechanisms.

4.1 Fast periodic-visual stimulation combined with frequency-tagging EEG

We applied this principle in oddball paradigms, where we presented images of neutral faces at a fast rate of 6 Hz, periodically interleaved with expressive faces every fifth image (i.e. 1.2 Hz oddball frequency). The periodic presentation at these predefined, yet, different, frequency rates generates distinguishable frequency tags for the base and oddball stimuli, allowing direct and objective quantification of the neural responses, indicating the discrimination of expressive faces amongst neutral faces. In addition, the rapid presentation enables a fast acquisition of reliable implicit expression-discrimination responses in only a few minutes of recording, with a high signal-to-noise ratio. Moreover, this technique allows the collection of discriminative responses, not only at a group level, but also at an individual level.

Hence, the implicit and straightforward nature of this approach, as well as the strength of its effects, pave the way to include populations that are often excluded from research due to cognitive or verbal constraints. In addition, the promising classification results for children with ASD demonstrate the potential of this technique to serve as a biomarker for socio-emotional processing difficulties. Considering the highly influenceable behavioural outcomes of facial emotion processing and the different underlying automatic emotion processing mechanisms, behavioural diagnoses could additionally be supported by objective implicit measures.

4.2 Facial mimicry recordings

To expand our understanding of the underlying automatic emotion processing mechanisms beyond the neural level and the gaze behaviour, we recorded the participants' facial mimicry while explicitly recognizing facial expressions. Despite the promising nature of this technique, there were some methodological issues that hamper drawing conclusions on the facial mimicry in boys with and without ASD.

First, given the high levels of sadness that were measured with FaceReader (Noldus, 2016) and have previously been reported in other studies with the same software (Suhr, 2017), results on the facial responses have to be interpreted with caution. Possibly, in our study, the camera angle might have induced FaceReader to mistakenly decode neutral faces as sad faces.

Second, notwithstanding the higher levels of sadness, the intensity values of all expressions were very low, except for neutral. This combination of high neutral scores and low expressive scores indicated little variation in the participants' facial expressions, and, accordingly, demonstrated no mapping between the observed and produced facial expressions. Therefore, we conclude that the Emotion Recognition Task (Kessels, 2014; Montagne, 2007) did not elicit clear facial responses and might thus not have been suited to investigate spontaneous facial mimicry. Possibly, the duration of the video clips was too short. However, previous studies investigating facial mimicry in children and adults with ASD did find clear facial responses to stimuli that were only presented for one or two seconds (Oberman et al., 2009; Schulte-Rüther et al., 2017). Yet, these studies applied EMG, which may be a more sensitive approach to detect even the subtlest changes in the facial muscles. Moreover, future studies should apply more evocative expressive stimuli, preferably within the context of real-life dyadic social interactions.

5. Future directions

Participants with ASD included in this study were all situated on the higher end of the spectrum, as we only included boys with an IQ > 70. Given that participants at the lower end of the spectrum often display more severe ASD-related symptoms (including social deficits), including these children in studies to implicitly measure their automatic emotion processing might provide a wealth of new information on their abilities and applied mechanisms. The use of implicit measures indeed allows to include these populations that are often excluded from research due to cognitive or verbal constraints.

Furthermore, the essential goal of facial emotion processing training (and social skills training in general) is to realize meaningful change in the individual's daily life (Berggren et al., 2018). However, until now, specific emotion processing training programs do improve emotion recognition, but no significant improvements have been reported on the social domain in general. Moreover, it remains uncertain to what extent treatment gains can be transferred to real-life social interactions (Berggren, 2018). Emotional faces generally do not display the emotion at its full intensity and the facial information in real-life naturalistic dyadic interactions is more dynamic (Hessels et al., 2018). Hence, these more subtle and rapid changes may demand different processing strategies as opposed to the processing of static images or dynamic movie clips. Therefore, applying these implicit measures in real-life dyadic social interactions might broaden our understanding of the automatic mechanisms even further.

6. Conclusion

With the present doctoral project, we aimed for a better understanding of the automatic processes underlying facial emotion processing in typically and atypically developing individuals. We conducted five studies in order to address the following objectives:

1. **To pinpoint the threshold of optimal spatial frequency information for the rapid automatic detection of fearful faces in healthy adult participants**

   Healthy adult participants rely mainly on HSF information: HSFs have an additive beneficial value when added to images containing only LSF and HSF information by itself allows neural detection of fearful faces. However, a slightly broader SF range is involved in explicit fear detection.

2. **To investigate different automatic emotion processes in school-aged boys with and without ASD**

   At a behavioural level, boys with and without ASD are equally capable to recognize emotions. However, the underlying automatic emotion processes differ slightly. In comparison to TD boys, we find:
   - an emotion-specific reduced neural sensitivity in boys with ASD. At a behavioural level, they compensate for this lower neural sensitivity by using a rule-based strategy
   - that boys with ASD apply a slightly different perceptual strategy (i.e. slightly more feature-based, slightly less exploratory and slightly less differentiated for different expressions), yet, they do not fail to attend to the most informative face area and extract the critical emotional information for accurate facial expression recognition

3. **To explore the effect of a single dose of oxytocin on the neural sensitivity to expressive faces in healthy adult participants**

   In healthy adult participants, the treatment effect of a single dose of oxytocin is mediated by person-dependent factors, such as social awareness. Oxytocin exerts its oxytocinergic effect mostly on individuals with more severe difficulties in the social domain, by attenuating their sensitivity for angry faces.

In sum, this doctoral dissertation contributed to the research field on multiple levels. First, we demonstrated that similar behavioural outcomes might originate from different underlying automatic emotion processing mechanisms. Second, we showed the importance of taking person-dependent factors into account. Third, we provided first indications that a single dose of intranasally administered oxytocin may enhance prosocial behaviour, by attenuating the sensitivity for negative emotions in individuals with most severe social deficits.

Overall, we add to the growing body of literature investigating one of the key components of social cognition: facial emotion processing. The findings reported in this dissertation demonstrate that there is more than meets the eye when explicitly processing facial expressions and emphasize the importance of taking these underlying mechanisms into account during therapy. Especially considering the heterogeneity within the autism spectrum, tailored interventions based on the underlying automatic emotion processes might result in optimal adjustment of this complex social behaviour.

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Appendices

Face processing in ASD

The studies described in Chapters 2, 3 and 4 were embedded in a larger study on face processing in boys with and without ASD. The following studies were conducted:

Social preference

- In this study, we applied a multi-input frequency-tagging EEG paradigm where we simultaneously presented images of faces and houses at two different frequencies (stimuli were counterbalanced for presentation frequency and presentation position on the left or right side of the screen) to investigate the social preference in boys with and without ASD. By also recording eye tracking data, we could examine both the overt orienting (via eye tracking) and the covert attention (via frequency-tagging EEG). We found that, while frequency-tagged neural responses were larger in response to faces than simultaneously presented houses in both groups, this effect was much larger in controls than in boys with ASD. This study is published in *Cortex*.
- In a follow-up study, a similar paradigm was employed, yet, here, the two streams of stimuli (faces versus houses; again tagged with a specific presentation frequency) were presented superimposed. This way, we controlled for possible effects of preferential looking, spatial attention, and disengagement. Results showed that in controls, the neural responses to faces were larger than those to houses, especially in occipito-temporal channels, while the responses to houses were larger over medial occipital channels. In the ASD group, however, faces and houses did not elicit significantly different neural responses in any of the regions. This study is published in *Frontiers in Psychiatry*.

Face and identity processing

- Both previously described studies indicated a reduced social bias / reduced saliency of faces in boys with ASD. Therefore, we wanted to investigate whether boys with ASD would be able to rapidly detect faces in a stream of objects. Here, images of objects were presented at a 6 Hz base rate, periodically interleaved every 5th image with a neutral face (i.e. oddball frequency of 1.2 Hz). In addition, we also investigated whether boys with and without ASD differentiate in their neural abilities to individuate unfamiliar faces by periodically embedding images of different individuals (again every 5th image, i.e. 1.2 Hz) in a rapidly presented stream of images of one individual (presented at 6 Hz). The faces were presented either upright or inverted. Results displayed no group difference in the neural responses indicating equal generic face categorization abilities in boys with and without ASD. The neural responses indexing individual face discrimination, however, were substantially reduced in the boys with ASD. This difference disappeared when faces were presented upside-down, due to the lack of significant face inversion effect in ASD. These results are published in *NeuroImage: Clinical*.

- In a next study, we investigated the saliency or importance of facial features when processing neutral faces using frequency-tagging EEG in combination with eye tracking. Participants watched fast flickering faces of which the upper and lower halves were presented at 6 Hz and 7.5 Hz or vice versa. This allowed us to disentangle the neural saliency of processing the eyes versus mouth region. We found that both groups looked longer to eyes than mouth, and this to a similar extent. Controls looked significantly more to the nose while the ASD boys looked more outside the face. At a neural level, we found similar brain responses in both groups to the upper or lower face half, but in the control group, neural responses to the lower face halves were larger than responses to the upper part. Face exploration dynamics showed that controls mostly maintained fixations within the same facial region, whereas boys with ASD switched more often between the face parts. This study is currently under review in *Molecular Autism*.

Facial expression processing

- In the study described in Chapter 2, we assessed the underlying neural nature of facial fear processing, and whether the neural sensitivity for fearful faces would be influenced by the orientation of the faces and by attentional focus to the eyes versus mouth. Boys with ASD were found to be less sensitive to rapidly and implicitly detect fearful faces, as compared to controls. Furthermore, both groups equally displayed the face inversion effect, suggesting the use of a combined holistic and feature-based face processing style, and both groups equally relied mainly on information from the mouth to detect the fearful expressions. This study is published in *Journal of Autism and Developmental Disorders*.

- In the study described in Chapter 3, we consolidated and expanded these findings by including anger, happiness and sadness as well, to investigate whether this lower neural sensitivity is emotion-specific or if it generalizes to all emotions. Our findings suggested a rather emotion-specific reduced neural sensitivity, as only fearful and angry faces evoked significantly lower brain responses in boys with ASD as compared to controls. This study is published in *Journal of Child Psychology and Psychiatry*.
- In the study described in Chapter 4, we simultaneously recorded eye gaze patterns and spontaneous facial mimicry of boys with and without ASD during an explicit expression recognition task. Our results suggest that boys with and without ASD employ similar eye gaze strategies to recognize facial expressions, albeit slightly less exploratory in the ASD group. Yet, this does not imply less efficient emotional information processing, considering the equal behavioral recognition performances. Pertaining to the facial mimicry, we found similar facial responses to emotional faces in both groups. This study is currently submitted to *Autism Research*.

In summary, although boys with ASD display a reduced social preference, they are able to rapidly detect faces (cfr. equal face categorization), possibly indicating that faces are less important or less salient for them than for typically developing boys. However, boys with ASD seem to have more difficulties with more subtle socio-communicative facial cues, such as identity and facial expression.

These paradigms were conducted in three different sessions, with the order of all paradigms counterbalanced within each session across participants:

- One session included paradigms on the face and identity processing, with the exception of the paradigm on the saliency of facial features
- One session included the facial expression paradigms discussed in Chapters 2 and 3
- One session included the paradigms on social preference, the saliency of facial features and the paradigm discussed in Chapter 4

About the author

Stephanie Van der Donck was born in Mortsel, Belgium on September 19th, 1988. In 2009, she graduated from the Karel de Grote Hogeschool Antwerpen, Belgium as a Professional Bachelor in Orthopedagogy, with a focus on Applied Youth Criminology. After following a two-year abridging program at Vrije Universiteit Brussel (VUB), she initiated a Master in Clinical Psychology, which she obtained magna cum laude in 2013. After graduation, she spent two months working as a psychologist in an orphanage for children with severe disabilities in Cuzco, Peru. However, as she always preferred the diagnostics to the therapy and counselling, the transition from the clinical world to academia was easily made.

In January 2014, she started her first job as a researcher at the faculty of Medical Sociology at VUB to investigate the reformation of the Belgian mental health care. When this two-year project ended, she transferred to KU Leuven to start her doctoral training at the then newly formed Center for Developmental Psychiatry at the Department of Neurosciences, under supervision of professor Bart Boets and co-supervision of professor Jean Steyaert and dr. Milena Dzhelyova. Her research focuses on the automatic underlying mechanisms of facial expression processing, both in healthy and clinical populations.

During her free time, she enjoys relaxing with a good book and a glass of wine, travelling, dancing and spending time with family and friends.

Curriculum Vitae

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Research funding, travel grants and awards

2020	**Postdoctoral mandate funding** (PDM) – KU Leuven
2020	**Travel Grant** – Fonds voor Wetenschappelijk Onderzoek (FWO)
2019	**Best poster award** – ‘Neurosense & Sense-ability’ workshop

Scientific Acknowledgements

This research was funded by grants of the Research Foundation Flanders: FWO, G0C7816N and an Excellence of Science (EOS) grant (G0E8718N; HUMVISCAT); and KU Leuven (grant C14/17/102).

I would like to thank professor Bruno Rossion for his indispensable input on the project, his experience and his genuine willingness to share his knowledge. I would also like to thank professor Valérie Goffaux and Kirsten Petras for their methodological support. Gratitude goes to the participants and their parents who contributed to our studies. Furthermore, I would like to thank Robine Hellemans (KU Leuven Master student) for her help during data collection in the context of her Master thesis (chapter 5). Special thanks also goes to the KU Leuven Master students Marte Biesmans and Elisabeth Heremans for providing me with the technology that facilitated data analysis (chapter 4).

Conflict of Interest

The author of this manuscript declares no potential conflict of interest for any of the contributing authors with respect to the research, authorship and/or publications.

Personal Contribution

The author of this dissertation was involved in all data collection, analysed and interpreted all data, and wrote each of the chapters of this manuscript. Professor Bart Boets and dr. Milena Dzhelyova provided senior mentorship on all papers included in the dissertation.

Chapter 1: SVDD, MD, JW and BB were involved in the conceptualization of the study and the design. TT was responsible for programming and for a large part of data collection (main experiment). SVDD collected the data of the control experiment. Both SVDD and TT analysed the data. SVDD prepared the original draft; TT, MD, JW and BB reviewed the manuscript and provided feedback. Given the large contribution of TT during paradigm set-up, data collection and data analysis, SVDD and TT share first authorship on the manuscript of chapter 1.

Chapter 2. BR and BB conceived of the study. SVDD, MD, SV, BR and BB participated in its design. HT and JS contributed to participant recruitment. SVDD, SV and HT collected the data. SVDD, MD and SV statistically analyzed and interpreted the data. SVDD wrote the manuscript and received feedback from all authors.

Chapter 3. SVDD and SV collected the data. JS contributed to participant recruitment. SVDD analyzed the data, with support of MD and BB. SSM and PC provided additional support for image analyses. SVDD wrote the manuscript. All authors have read the manuscript and provided feedback.

Chapter 4. SVDD and SV collected the data. JS was involved in recruiting the participants. SVDD analyzed and interpreted the data, with support of SV. PC and SSM were involved in the preprocessing of the facial mimicry data. SVDD wrote the manuscript, with assistance of BB.

Chapter 5. KA and BB conceived of the study and participated in its design. Data was mainly gathered by TD, with additional support of SVDD and SV. SVDD did all statistical analyses, with assistance of BB and KA. SVDD wrote the manuscript. All authors have read the manuscript and provided feedback.