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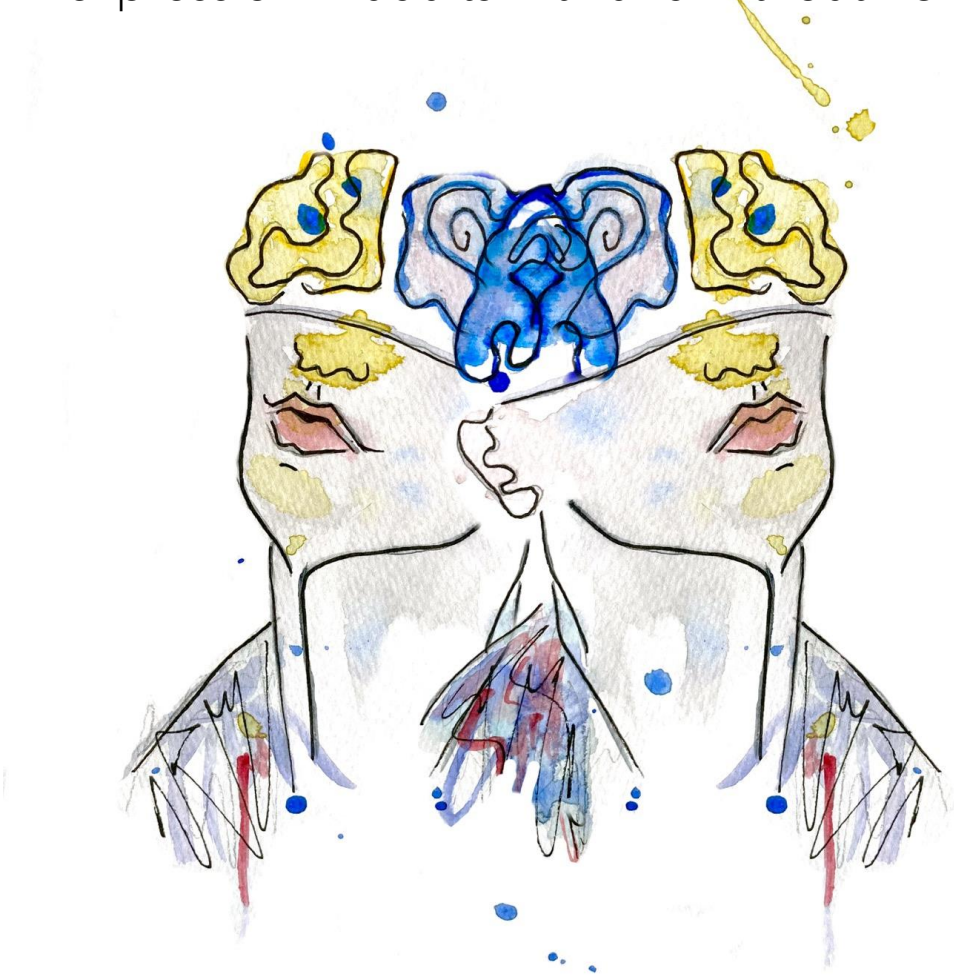
FACULTEIT PSYCHOLOGIE EN
PEDAGOGISCHE WETENSCHAPPEN

Faces in the autistic brain

Neural processing of facial identity and facial expression in adults with and without ASD



Michelle Hendriks

Doctoral thesis offered to obtain the degree of Doctor of Psychology (PhD)

Under supervision of prof. dr. Hans Op de Beeck, prof. dr. Bart Boets & dr. Felipe Pegado

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Brain and Cognition

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Cover art created by Rachel Carpentier.

Summary

Face processing, including the processing of facial identities and expressions, has been argued to be of key importance to successful social communication. In that light, it is not surprising that impaired face processing in autism spectrum disorder (ASD) has been suggested as a source of ASD-related social difficulties. In this dissertation, I focus on face processing in the ASD population. The neural basis of face processing is discussed, introducing dominant models and proposed adaptations. In addition, I describe face processing research in the ASD population, and potential mechanism to explain ASD-related atypicalities. I present two studies in which we investigated the processing of facial identity and expression in high functioning adults with and without ASD. In the first study, functional magnetic resonance imaging (fMRI) was used in combination with a single paradigm comprising dynamic facial stimuli. We ran behavioural, univariate, multivariate, adaptation and functional connectivity analyses. In the second study, frequency-tagging electroencephalography (EEG) was used in combination with fast periodic visual stimulation (FPVS) of faces, employing two separate paradigms (i.e., one identity and one expression paradigm) with static facial stimuli. General neural synchronisation to faces as well as neural sensitivity to changes in facial identity and expression were investigated. These two studies yielded no differences between individuals with and without ASD in terms of behavioural face processing performance, neural activity levels while processing faces, neural representations of facial identities and expressions, release from adaptation to facial identities and expressions, general neural synchronisation to faces, or sensitivity to changes in facial identities and expressions. We only observed a minor difference between the groups in how the amygdala is connected to two low-level regions in the face processing network: the inferior occipital cortex and V1. I discuss these results in the broader context of the literature and conclude that high functioning adults with and without ASD process facial identities and expression very similarly.

Neural face processing was studied using fMRI as well as EEG. Therefore, I describe the workings behind both techniques, respective strengths and limitations, and several analysis approaches. Furthermore, I present a study in which one pre-processing step in the analysis of fMRI-data was investigated. More specifically, I describe how results of correlational multi-voxel pattern analyses (MVPA) are influenced by various levels of spatial smoothing. Our findings suggest that smoothing has a minor positive effect on the MVPA results.

Samenvatting

Gezichtsverwerking, waaronder de verwerking van gelaatsidentiteit en -expressie, wordt vooropgesteld een grote rol te spelen in succesvolle communicatie. Problemen met de verwerking van gezichten worden gesuggereerd aan de basis te liggen van de sociale moeilijkheden die personen met autismespectrumstoornis (ASS) ervaren. In deze dissertatie focus ik op gezichtsverwerking in ASS. Ik bespreek de neurale basis van gezichtsverwerking en introduceer dominante modellen en mogelijke aanpassingen, alsook gezichtsverwerkingsonderzoek in de ASS-populatie. Ik stel twee studies voor waarin de verwerking van gelaatsidentiteiten en -expressies onderzocht werd bij volwassen mannen met en zonder ASS. In de eerste studie werd fMRI gebruikt in combinatie met één paradigma waarin bewegende gezichten gepresenteerd werden. We deden gedrags-, univariate, multivariate, adaptatie en functionele connectiviteitsanalyses. In de tweede studie gebruikten we EEG in combinatie met de snelle presentatie van bewegingloze gezichten in twee afzonderlijke paradigma's (één identiteits- en één expressieparadigma). We onderzochten de algemene neurale synchronisatie met gepresenteerde gezichten en de neurale sensitiviteit voor veranderingen in gelaatsidentiteit en -expressie. We vonden geen verschillen tussen personen met en zonder ASS wat betreft gedragsprestaties, neurale activiteitsniveaus, neurale representaties, herstel van adaptie van gelaatsidentiteit- en expressie, algemene neurale synchronisatie met gezichten, of sensitiviteit voor veranderingen in gelaatsidentiteit en -expressie. We vonden slechts een gering verschil tussen de groepen met betrekking tot de manier waarop de amygdala functioneel verbonden is met twee low-level hersengebieden in het gezichtsverwerkingsnetwerk: de inferieure occipitale cortex en de primaire visuele cortex. Ik plaats deze resultaten in de bredere gezichtsverwerkingsliteratuur, en concludeer dat hoog functionerende volwassenen met en zonder ASS gelaatsidentiteiten en -expressies zeer gelijkaardig verwerken vergeleken met neurotypische volwassenen.

Om gezichtsverwerking te onderzoeken, maakten we gebruik van fMRI en EEG. Ik bespreek daarom hoe deze technieken functioneren, hun sterktes en zwaktes, alsook verschillende analyses. Daarnaast stel ik een studie voor waarin één pre-processing stap in de analyse van fMRI data onderzocht werd. Meer concreet beschrijf ik hoe de resultaten van correlationele MVPA beïnvloed worden door verschillende niveaus van smoothing. Onze resultaten suggereren dat smoothing een gering, positief effect heeft op MVPA-resultaten.

Preface

Before you lies the doctoral dissertation 'Faces in the autistic brain: neural processing of facial identity and facial expression in adults with and without autism spectrum disorder', the result of almost five years of research. Five years ago, I was offered the chance to start a PhD in psychology, on two subjects of great interest to me: neuroscience and autism spectrum disorder. It really was a dream come true. Although it was not always a walk in the park, I am happy and proud to present this dissertation to the world. It took a village, and I would like to express my sincerest gratitude to everyone involved.

I want to start by thanking professor Op de Beeck for offering me the chance to start this adventure and guide me along the way. Hans, your powers of observation, scientific insight and knowledge often helped me, and taught me a lot. Thank you for believing in me, sometimes even more so than I believed in myself. In addition, I want to thank professor Boets. Bart, your enthusiasm and optimism were contagious. Thank you for the chance to work in close collaboration with your lab, I learned a lot. Felipe, I also want to thank you for mentoring me during my internship and throughout this doctoral period.

I would like to express my gratitude to the members of the supervisory and midterm committees that evaluated my work throughout this doctoral period, as well as the jury members of this dissertation: prof. dr. Bhismadev Chakrabarti, dr. Haemy Lee Masson, dr. Laurie-Anne Sapey-Triomphe, dr. Sander Van de Cruys, prof. dr. Jan Van den Stock. Thank you for your time and effort, as well as for your helpful feedback and suggestions.

Next, I want to thank my colleagues, the lot of you. To my 'fun office' girls: thanks for all the help, advise and courage you gave me. Thanks for all the laughs, tea-time talks about every topic and more, and of course for our wall, which I will never forget. To all other (ex-)LBP'ers: thanks for all the (pre-covid) lunchbreaks, retreats, and all the laughs and talks. A special thanks to Jessica Bulthé for her help with data-analysis when I just started my PhD. To all my colleagues at the CDP: thank you for your kindness, advice, and help. Thanks to Sofie and Stephanie, for their help with paradigms, analyses and much more. A special thanks to Silke, as it would not have been possible to finish this thesis without her help, I will forever be grateful! Last but certainly not least, a very special thanks to Anna for always being there. Your status changed from 'colleague' to 'friend' pretty quickly, maybe even from the moment we met.

Ook zou ik iedereen die heeft deelgenomen aan de onderzoeken in deze thesis hartelijk willen bedanken. Jullie zijn de echte helden die dit mogelijk hebben gemaakt. Bedankt aan alle collega's en vrienden die hebben deelgenomen, en zeker ook aan alle andere deelnemers. Zonder jullie was het nooit gelukt! Ook bedankt aan iedereen die op welke manier dan ook heeft bijgedragen aan de rekrutering van deelnemers. Nicky, voor de hulp tijdens het contacteren van personen uit de database van LBP en zóveel meer. Jean en Annelies, voor het contacteren van deelnemers met ASS vanuit het Expertise Centrum Autisme. Het Atmosfeer-team voor de hulp bij het rekruteren van deelnemers met ASS vanuit het Universitair Psychiatrisch centrum Kortenberg. Allen bedankt!

Als laatste zou ik mijn vrienden en familie willen bedanken. Mama, papa, dankjewel voor alle steun en de thuis die ik altijd heb in Kinrooi. Ook dankjewel om dag in, dag uit goed voor mijn paardjes te zorgen, dat apprecieer ik énorm. Aan al mijn lieve vriendjes: dankjewel om er voor mij te zijn. Aan al degenen die voor plezier en afleiding zorgden, op welke manier dan ook: bedankt om mijn hoofd leeg te maken en mij nieuwe energie te geven. Aan degenen die me af en toe eens durfden vragen hoe mijn doctoraat ervoor stond: bedankt om te luisteren en me hoop en vertrouwen te geven dat het zou lukken! Een speciaal bedankje aan het beste, liefste buurtje, Rachel, die de cover heeft ontworpen. We zijn samen opgegroeid, en nu is ons werk gebundeld, hoe leuk is dat?! Het meest speciale bedankje gaat naar de meest speciale persoon. Niels, bedankt dat je er altijd voor mij bent. Jij bent de enige persoon die ieder moment van dit doctoraat met mij meegeleefd en meebeleefd heeft. Jouw nuchtere kijk op zaken heeft me soms gefrustreerd, maar heel vaak geholpen. Bedankt ook voor het nalezen van dit werk, de eerste én de tweede keer. Je ben de beste! Jullie zijn allemaal de beste!

Michelle Hendriks
Paal, juni 2021

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List of often used abbreviations

ASD	Autism spectrum disorder
BOLD	Blood oxygenation level dependent
EEG	Electroencephalography
FFA	Fusiform face area (in fusiform cortex)
fMRI	Functional magnetic resonance imaging
FPVS	Fast periodic visual stimulation
GLM	General linear model
LOT	Left occipitotemporal cortex
MO	Medial occipital cortex
MVPA	Multi-voxel pattern analysis
NT	Neurotypical (i.e., without ASD in this case)
OFA	Occipital face area (in the inferior occipital cortex)
ROI	Region of interest
ROT	Right occipitotemporal cortex
STS	Superior temporal sulcus
V1	Primary visual cortex

Dissertation outline

This doctoral project revolves around two central themes: neuroimaging and face processing in autism spectrum disorders (ASD), corresponding to Part I and Part II of this dissertation.

Part I: Experimental techniques.

In this part, I discuss the used neuroimaging techniques: functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). This part includes one published study about the effect of a single pre-processing step – spatial smoothing - on the results of multi-voxel pattern analyses of fMRI data (Chapter 2).

Chapter 1: Introduction to experimental techniques

In this first chapter, I introduce the neuroimaging techniques used throughout this doctoral dissertation. The workings behind both techniques are explained, as well as their strengths and limitations. In addition, several analysis approaches are discussed. The background provided in this chapter will help the reader throughout the remainder of this dissertation.

Chapter 2: The effect of spatial smoothing on the results of multi-voxel pattern analyses

In a second chapter, I report a first published study. In this study, we investigated how one step in the pre-processing of fMRI data influenced the results of correlational multi-voxel pattern analyses. Often, choices made during the analyses of neuroimaging data seem arbitrary. We wanted to study whether these 'arbitrary' choices impact the results. In addition, answering the question whether the amount of smoothing affects MVPA results has further implications for the debate on so-called hyperacuity: the suggestion that MVPA can be used to pick up signals that are organised at a scale finer than the voxel size.

Part II: Face processing in autism spectrum disorder

In this part, I discuss the processing of facial identity and expression in individuals with and without ASD. The aim was to advance the understanding of neural processes involved in face processing, and how these processes are different in adults with ASD. This part includes one published study (Chapter 4) and one study in preparation for publication (Chapter 5). The dissertation in ended in a general discussion of the results (Chapter 6).

Chapter 3: Introduction to face processing and autism spectrum disorder

In the third chapter, I introduce the literature on face processing, including various proposed models throughout the years. In addition, the diagnosis of autism spectrum disorder is characterised, including diagnostic features, prevalence, and several accounts to explain ASD. Furthermore, the atypical face processing of individuals with ASD is outlined and neuroimaging literature is described, including fMRI as well as EEG studies.

Chapter 4:
Processing of facial identity and expression in adults with and without ASD using fMRI

In the fourth chapter, I report a second published study. In this study, fMRI was used as a tool to study how the identity and expression of faces are processed on a neural level and whether this is different for individuals with ASD. To achieve this, we conducted univariate, multivariate, adaptation and functional connectivity analyses, and compared results between individuals with and without ASD.

Chapter 5:
Processing of facial identity and expression in adults with and without ASD using EEG

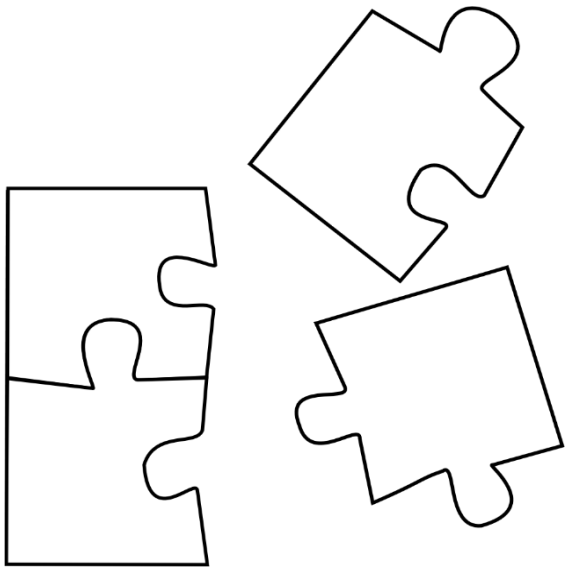
In the fifth chapter, I report a study in preparation for publication. In this study, EEG was used as a tool to study the neural processing of facial identity and expression and whether these processes are different for adults with and without ASD. Accordingly, a frequency-tagging EEG approach was used in combination with the fast periodic visual presentation of faces. We contrasted the results between adults with ASD and neurotypicals.

Chapter 6: Discussion on face processing

I conclude this dissertation in a discussion of the two abovementioned studies. In this chapter, the findings and its implications are summarised and placed in the available face processing literature. In addition, possibilities for future research are discussed. Finally, the dissertation ends with a general conclusion.

PART I

Experimental techniques



Overview Part I

The first part of this dissertation is rather technical in nature. In Chapter 1, I thorougly discuss two often-used, non-invasive neuro-imaging techniques: functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). Both fMRI and EEG were used to acquire data throughout this doctoral period, and it is important that readers are introduced to both techniques. In addition to the workings behind fMRI and EEG, I describe their respective strengths and limitations, as well as several analysis approaches. In Chapter 2, I focus on one particular step in the analysis of fMRI data: spatial smoothing, which is often used to increase the signal-to-noise ratio of the data. More specifically, I present a study in which the effect of spatial smoothing on the results of one specific fMRI analysis approach – correlational multi-voxel pattern analysis- was investigated.

Chapter 1

Introduction to experimental techniques

Summary Chapter 1

Throughout the course of this doctoral period, I used both functional magnetic resonance imaging and electroencephalography to investigate neural responses. In this chapter, both techniques are discussed.

First, the workings behind functional magnetic resonance imaging (fMRI) are outlined. In recent cognitive neuroscience research, fMRI has often been used to study the human brain. Using fMRI, we can investigate the brain in a non-invasive manner with an excellent spatial resolution. Here, I describe its advantages and limitations, as well as the different kinds of analyses, restricted to the ones used during the course of this PhD. These include univariate, multivariate, adaptation and functional connectivity analyses.

Secondly, the workings behind electroencephalography (EEG) are outlined. EEG has been used for nearly a century to study the brain (İnce et al., 2020; Tudor et al., 2005). Using EEG, we can study neural activation in a non-invasive manner with a high temporal resolution. Here, too, I describe the advantages and limitations, and the analysis approach used throughout this doctoral period, namely fast periodic visual stimulation in combination with frequency-tagging EEG.

1. Functional Magnetic Resonance Imaging (fMRI)

1.1. How does fMRI work?

Magnetic resonance imaging (MRI) works because our bodies largely consist of water. The water molecules in our body are affected by the extraordinarily strong magnetic field in the MRI scanner. In principle, this field is always present, which is why you must be incredibly careful around an MRI scanner. Researchers can further manipulate the water molecules by using energy in the form of radio frequency (RF) waves. After the energy of RF waves has been absorbed by the water molecules, they 'flip' back while releasing the absorbed energy: a process called magnetic resonance. This release of energy is picked up by the scanner (Möllenhoff et al., 2012). The key is that different tissues release the absorbed energy at a different rate. This contrast between tissues is used to make the magnetic resonance image (Hendrick et al., 1984). For example, cerebrospinal fluid contains a lot more water than the largely myelinated white matter, which again has a different viscosity than grey matter. Because these tissues have distinct consistencies, they behave distinctively when releasing energy, and show up differently on the image. A structural image of the brain is born.

The next step is looking at activation in the brain. *Functional magnetic resonance imaging* (fMRI) relies upon the fact that active neurons need oxygen. Oxygen is transported by a molecule called haemoglobin, that can be found in one of two states: oxygenated haemoglobin (oxyhaemoglobin) while carrying oxygen, or deoxygenated haemoglobin (deoxyhaemoglobin) once the oxygen has been released. The magnetic properties of these states differ: oxygenated blood is diamagnetic, while deoxygenated blood is paramagnetic (i.e., attracted to a magnet) (Pauling & Coryell, 1936; Thulborn et al., 1982). Hence, if the proportion of deoxyhaemoglobin in the blood rises, its magnetic susceptibility increases. In addition, when brain areas become active, blood flow increases: the so-called haemodynamic response (Poldrack et al., 2011). Thus, both the composition and the volume of blood will change when a brain region is activated. Paradoxically, blood in active brain regions will have a higher level of oxyhaemoglobin than blood in inactive areas, because the increase in blood volume is relatively larger than the increased uptake of

oxygen (Fox & Raichle, 1986). The contrast in ratio of oxy- versus deoxyhaemoglobin between active and inactive regions can therefore be used to obtain a functional image. The signal derived from this contrast is called the 'blood oxygenation level dependent' (BOLD) signal (Ogawa et al., 1990).

1.2. Strengths of fMRI

fMRI data has an outstanding spatial resolution, meaning the source of activation can be pinpointed with an accuracy of at least several cubic millimetres. With this accuracy, it is possible to locate separate brain regions with a good amount of precision. fMRI has therefore been used before neurosurgery to map motor and language areas that should stay intact (Yoo et al., 2004). The exact spatial resolution of fMRI data depends on several factors, such as the field strength of the magnet and the needed brain coverage (e.g., whole brain, only a certain lobe, or only a specific structure). Furthermore, the spatial resolution can be enhanced by particular pulse sequences (Feinberg & Yacoub, 2012). However, the spatial resolution is also limited by so-called 'draining veins'. Since blood is constantly flowing, the BOLD-signal changes can occur several millimetres away from the actual source of activation (Mullinger & Bowtell, 2011).

Using fMRI, we can look at subcortical brain regions of interest. fMRI is therefore utmost suitable for studies investigating the brain beyond the cerebral cortex, including regions deep within the brain. An example of a brain area of interest from this dissertation is the amygdala, a region that is not only fairly small but also located far beneath the cortex, deep within the temporal lobe (Sah et al., 2003). Current advancements in the field are optimising data acquisition, assuring that cortical and subcortical areas can be mapped with excellent spatial resolution (e.g., Miletić et al., 2020).

1.3. Limitations of fMRI

Firstly, the temporal resolution of fMRI is rather low. The BOLD-signal is only an indirect measure of neural activity, derived from the haemodynamic response. The haemodynamic response is relatively slow, only reaching a maximum increase in blood flow 5 seconds after neural activation (Poldrack et al., 2011) and a peak in the BOLD-signal 5-8 seconds after stimulus onset (Buxton, 2009). Consequently, modelling the precise time-course of the neural activation with an accuracy of milliseconds does not seem possible (Friston et al.,

1998; Kim et al., 1997). However, models to estimate neural activation from fMRI signals have improved, and the slowness of the scanner (i.e., time to scan one full image, or repetition time) became a limit to the temporal resolution. Recently, researchers have been developing ways to decrease the acquisition time of a single image and managed to successfully increase the temporal resolution of fMRI data (Yoo et al., 2018).

A second disadvantage of fMRI is the cost of data acquisition. An MRI scanner costs significantly more than an EEG system. Understandably, researchers and research groups often do not have sufficient funds to buy their own MRI machine. Instead, they 'rent' hospital-owned MRI scanners in payment by the hour. This is rather expensive: acquiring data of fifty participants can cost more than buying a complete EEG set-up. However, based on personal experience, the upside of this price-tag is excellent and swift technical support.

Finally, it can be challenging to find participants that are able to stay in a small space for a long period of time without moving. This prerequisite of fMRI data acquisition can create a bias in included populations, as individuals with more severe psychiatric conditions often find it difficult not to move in the scanner (Greene et al., 2016). Specific to autism spectrum disorders, researchers often only include high functioning individuals with ASD. Unfortunately, this jeopardises the generalisability of findings to the ASD population as a whole.

1.4. Pre-processing of fMRI data

After acquiring fMRI data, a lot of analysis steps are needed to make the data interpretable. A first major step is to ensure that we have acquired high-quality data. It is essential that the images contain all relevant brain regions without distortions. A distortion can be caused by everyday items, such as a hair elastic with a tiny piece of metal causing a big 'hole' in the image. Next, the data is pre-processed to prepare it for further analyses. Pre-processing can be performed in a myriad of ways. Different software packages and research groups often use (slightly) different pre-processing pipelines, using the pre-processing steps they consider important in the order they believe to be preferable. Importantly, the pre-processing pipeline presented here is only one of these many possibilities. More specifically, I describe the pre-processing pipeline used in the fMRI analyses presented in this dissertation. We started by correcting for slice timing. Since a whole-brain fMRI image is acquired in slices (i.e., not at once), there is a lag of several seconds between the first and

the last acquired slice for which we need to correct. Secondly, we corrected for head motion by realigning all functional images to one reference image. The parameters gathered during this pre-processing step are also used to check for excessive movements. When a participant moved more than the size of one voxel throughout the acquisition of a functional image, the data were discarded. Thirdly, to be able to map functional findings on anatomical space, we co-registered the anatomical scans with functional images. Fourthly, we normalised the data across all participants to be able to perform analyses on a group level. For this purpose, we transformed the data to MNI space. Finally, the images were smoothed using a Gaussian kernel. This results in a blurrier image, because the value in every voxel has been averaged with its neighbouring voxels. This last step suppresses noise and diminishes slight functional and anatomical differences between participants. In Chapter 2, spatial smoothing is the topic of interest. Figure 1.1 illustrates functional images throughout the pre-processing pipeline, with different levels of smoothing.

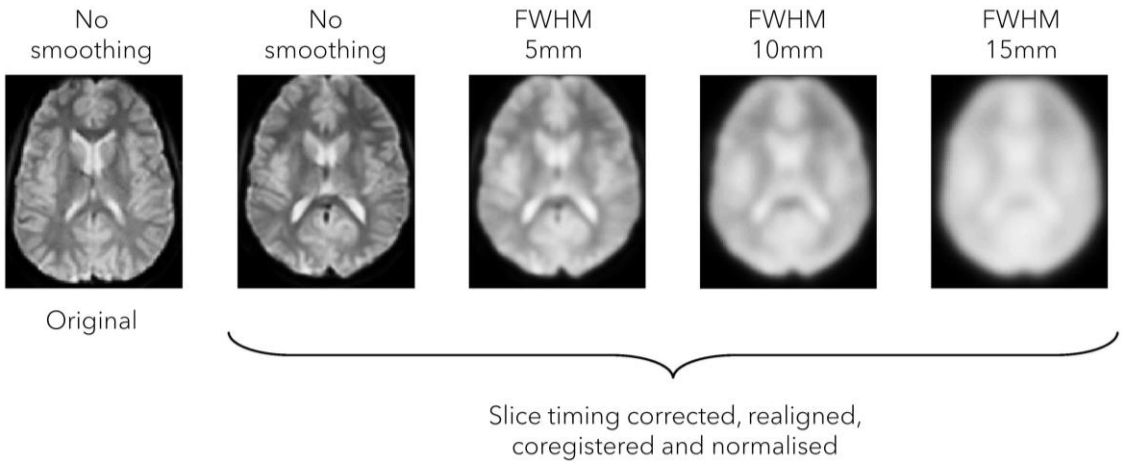


Figure 1.1. Functional scans before and after pre-processing, displaying different levels of smoothing. Left image shows an original image, without any pre-processing performed on it. The next 4 images have undergone slice-timing corrections, realignment, co-registration, and normalisation, and show several levels of smoothing.

1.5. General Linear Model

After pre-processing the data, we use a general linear model (GLM) to estimate which brain areas respond to different task conditions. More specifically, the BOLD response in every voxel is modelled as a dependent variable, while the conditions within the experiment are modelled as independent variables. Motion parameters computed during the pre-

processing step of realignment are used as covariates in the model to account for minor head movements. The contribution of every experimental condition to the BOLD signal is estimated using the GLM, resulting in a map of beta-values. This beta-weights map indicates the level of activity in every voxel during a specific task condition.

1.6. Univariate analysis

Univariate analyses allow us to study which brain regions are active when someone is performing a specific task, by comparing the activation in a certain brain area in one condition (for example an experimental condition) to the activation of this brain region in another condition or baseline (for example the fixation condition). In practice, the baseline activation is subtracted from the activation during the experimental condition, and average activation levels within brain regions are computed. In a next step, the activation within a certain brain region can be averaged across individuals and compared between groups (Figure 1.2). In this dissertation, we are indeed interested in a difference between groups. In Chapter 4, I report this univariate analysis, which was used to investigate whether individuals with ASD show a different level of activation to faces than neurotypical individuals in several face-responsive brain areas.

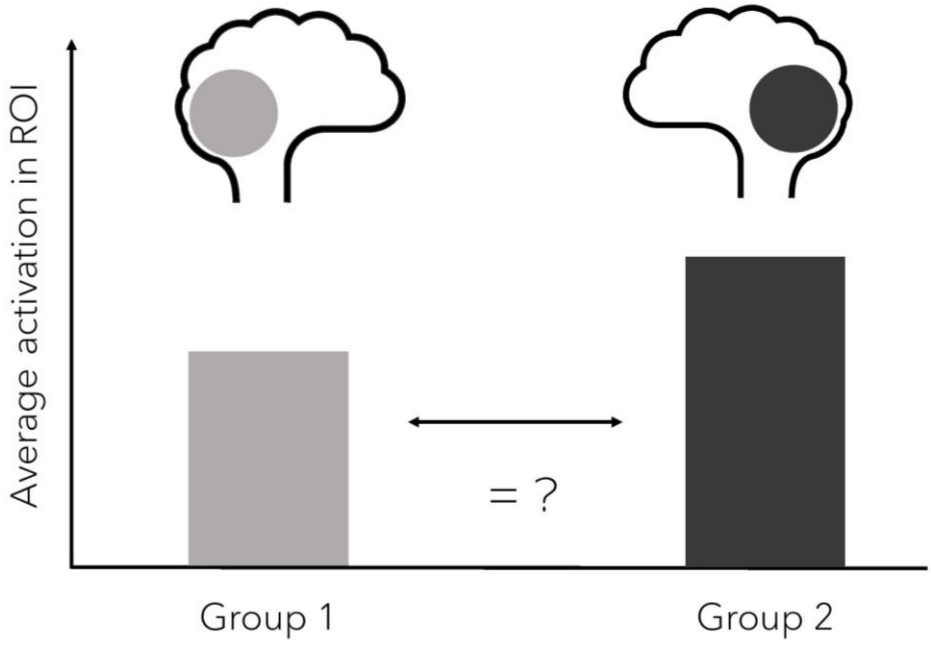


Figure 1.2. Univariate analysis. The average activation within a brain area across all voxels is calculated for a specific condition. Next, we can compare the average activation between groups.

1.7. Multivariate analysis

Multivariate analyses allow us to study the patterns of activation within brain regions, instead of looking at the average activation of certain brain areas. These methods are known under names such as multi-voxel pattern analysis (MVPA), brain decoding, and representational similarity analysis (RSA) (Haynes & Rees, 2006; Kriegeskorte et al., 2008; Norman et al., 2006). It has been suggested that this approach offers a more sensitive measure to pinpoint how information is represented in the brain, compared to univariate analyses (Haxby et al., 2001; Koster-Hale et al., 2013). There are several multivariate approaches, but I only describe the approaches used in this dissertation: correlational MVPA and decoding MVPA.

Correlational MVPA starts with splitting the data into two halves. Next, we compute the correlations between activation patterns of same conditions and the correlations between activation patterns of different conditions (Figure 1.3).

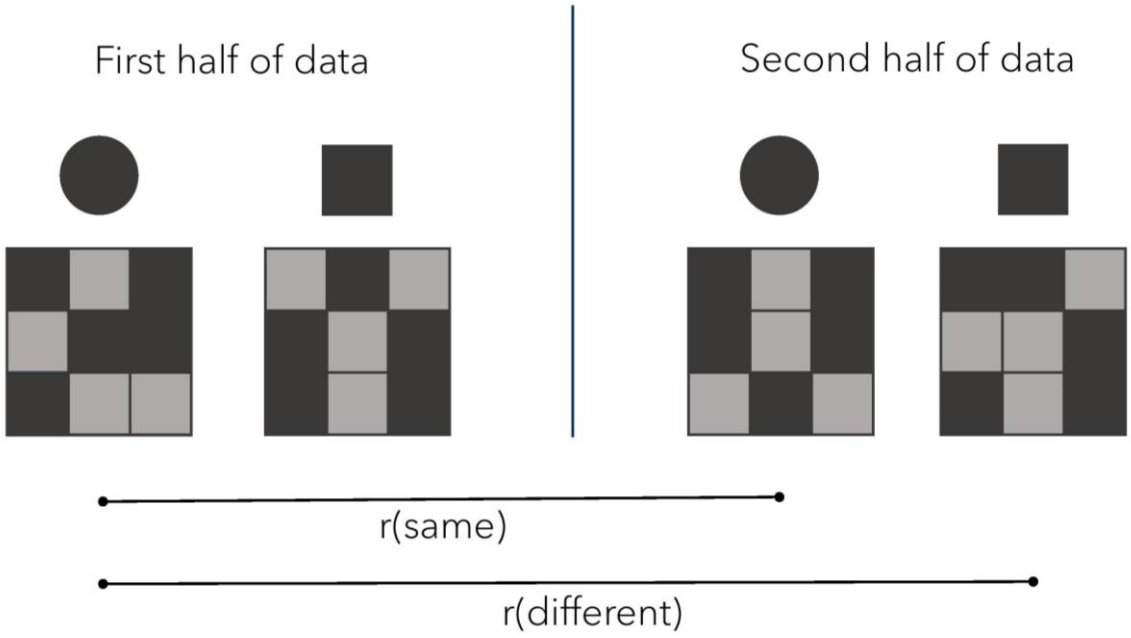


Figure 1.3. Multi-voxel pattern analysis, correlational approach. The data are split in half and correlations are computed between same conditions and between different conditions in the two halves of the data. If conditions can be distinguished based on neural patterns, the correlations between same conditions will be consistently higher than the correlations between different conditions.

For example: we compute the correlation between 'circle' activation patterns in the first part of the data and 'circle' activation patterns in the second part of the data, resulting in a correlation between same conditions. Next, we compute the correlation between 'circle' activation patterns in the first part and 'square' activation patterns in the second part, resulting in a correlation between different conditions. If our brains can notice the difference between conditions, we expect the correlation between same conditions to be significantly higher than the correlation between different conditions. In other words, if the 'circle' activation patterns are consistently more similar to one another and consistently more distinct from 'square' activation patterns, we can say that circles and squares are represented differently in the brain. In Chapter 2, we use correlational MVPA to investigate whether the results of this MVPA approach are influenced by distinct levels of smoothing.

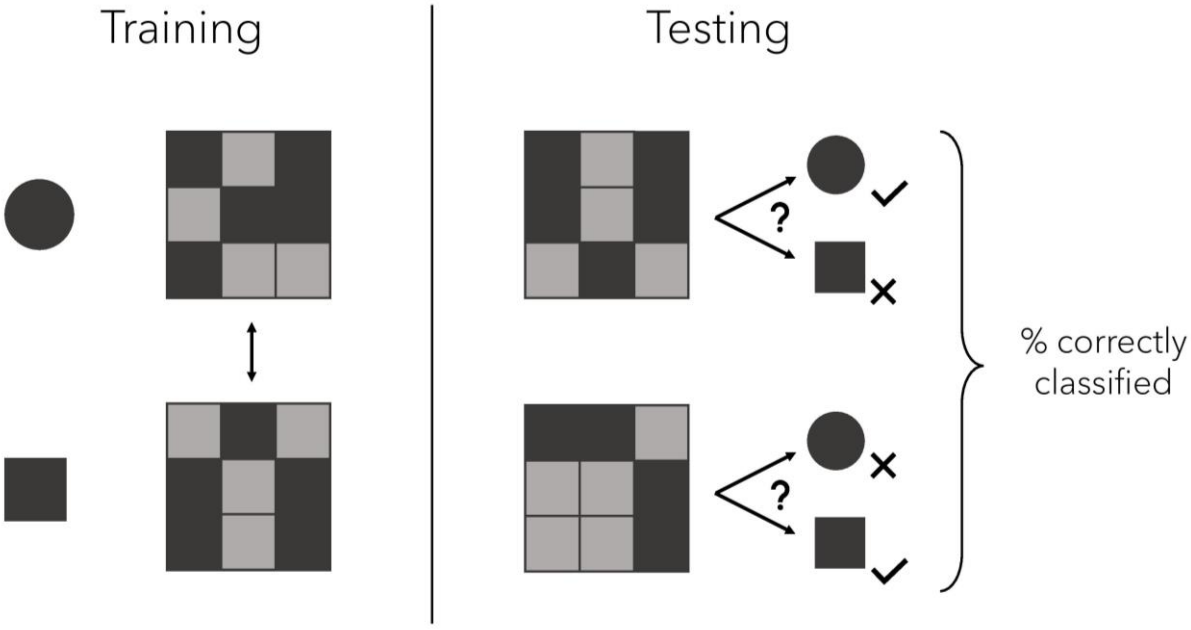


Figure 1.4. Multi-voxel pattern analysis, decoding approach. First, a classifier is trained to distinguish between two conditions, in this case between a circle and a square. After training, the model is tested using new data. If the conditions can be distinguished based on the neural activation patterns, the model will classify neural patterns with an accuracy of more than the chance-level of 50 percent.

Decoding MVPA is a second approach used in this dissertation. Again, we divide the data in two: 70% of the data is used to train a model, while the other 30% is used to test the model. During training, a model learns to distinguish different conditions based on the activation

patterns within a certain region of interest (ROI) (Figure 1.4). A 'circle' activation pattern might, for instance, have active voxels in the upper right part of the pattern, while a 'square' activation pattern has active voxels in the lower right part of the pattern. The model looks for these kinds of diagnostic features to rely on to make a distinction. When the model is sufficiently trained, we test whether it can reliably make the distinction between the trained conditions. For this purpose, we use the final 30% of the data, which is new to the model. If the model performs above chance level (50%), we can conclude that the conditions are distinguishable based on the neural activation patterns in a certain ROI. In Chapter 4, we use this approach to study the neural representations of facial identity and facial expression.

1.8. Adaptation analysis

Adaptation allows us to study whether brain areas are sensitive to certain conditions, by using something as simple as repetition (Grill-Spector et al., 2006; Grill-Spector & Malach, 2001).

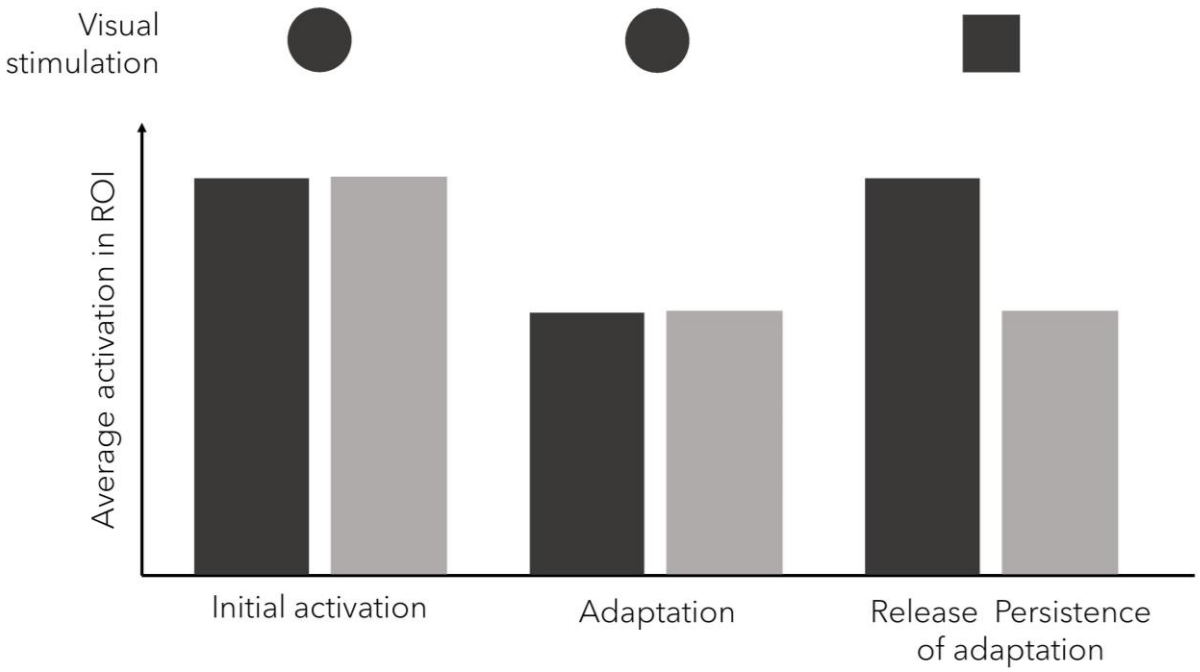


Figure 1.5. Adaptation analysis. Adaptation is measured as a decrease in neural activation when a stimulus (in this case a circle) is repeated. Presentation of a different stimulus can result in (1) release of adaptation (in black), indicating the brain region is sensitive for the change in stimulus or (2) persistence of adaptation (in grey) indicating the investigated brain area is not sensitive to this change.

This analysis hinges on the fact that neurons adapt to repeated presentation of the same stimulus or stimulus condition: the activation level decreases. When the stimulation is changed to a different condition, two outcomes are possible. Either the activation level recovers, indicating the region is sensitive to the change in condition; or it remains adapted, implying the brain area is invariant to the changed property (Figure 1.5). If, for instance, circles are shown subsequently, neurons will show a decrease in activity. When the next stimulus is a square, we can see a release from adaptation indicating the area is sensitive to the presented form, or a persistence in adaptation when the area is not sensitive to this change. In Chapter 4, we use this analysis to study the sensitivity of face-responsive brain areas to facial identity and facial expression.

1.9. Functional connectivity analysis

Functional connectivity analyses allow us to study which brain areas communicate with one another by computing temporal correlations between brain regions (Friston, 2011). A temporal correlation is believed to reflect functional communication among these regions (Gillebert & Mantini, 2013). In practice, we calculate the average BOLD time course within every brain area, and compute pairwise temporal correlations between the regions (Figure 1.6). A significant correlation between two regions indicates these regions are functionally connected. In Chapter 4, we use this analysis to study the functional connectivity within the face processing network and the difference between individuals with and without ASD.

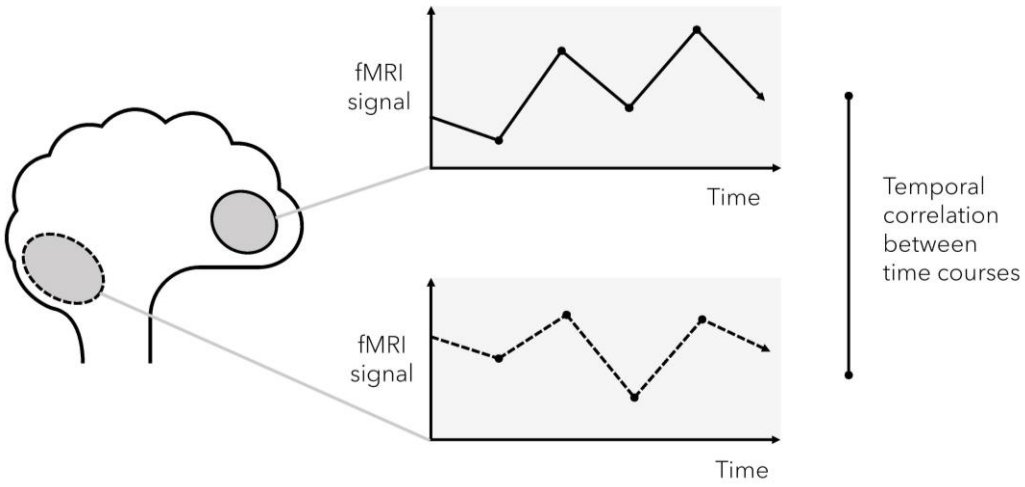


Figure 1.6. Functional connectivity analysis. Average time courses are computed within brain regions, after which a temporal correlation between these time courses is calculated. If temporally correlated, brain areas are thought to be functionally connected.

2. Electroencephalography (EEG)

2.1. How does EEG work?

When undergoing EEG, a cap with electrodes is placed on the head. Every electrode measures the brain's electrical field, which results from signals passing from one active neuron to the next. Because neural populations fire simultaneously, the electrical current becomes powerful enough to be picked up outside of the skull (Biasiucci et al., 2019). Over time, the electrical current fluctuates and forms complex patterns of signals with different amplitudes and frequencies (Cohen, 2017). This results in a record of electrical oscillations originating from within the brain (Nunez & Srinivasan, 2006a). The goal is to investigate how these neural oscillations relate to neural processes (Cohen, 2017). In Chapter 5, we investigate how the neural oscillations relate to face processing, and whether this differs between individuals with and without ASD.

2.2. Strengths of EEG

Firstly, EEG has a high temporal resolution, as the data reflect a moment-by-moment recording of brain activity. The temporal resolution depends on the sampling rate but is often of the order of milliseconds (Mullinger & Bowtell, 2011). In Chapter 5, we used a sampling rate of 512 Hz, meaning more than 500 datapoints were acquired every second. In other words, a datapoint was recorded roughly every 2 milliseconds, which can count as a high temporal resolution indeed.

Another advantage of EEG is – depending on which paradigms are used - that data collection of several studies can be combined. Using fast periodic stimulation paradigms, we unified the data acquisition of three studies, among which the data reported in Chapter 5. Although this seems perfect, researchers should be mindful about which studies are coupled: it might be advantageous to only combine studies with the exact same inclusion and exclusion criteria. In practice, this means only coupling studies investigating the same modality in precisely the same population. Unifying different modalities in data acquisition

can cause problems with recruitment, as participants might be considered for one but not the other study.

Finally, when compared to fMRI, EEG has the advantageous ability to study a broader population. Participants do not have to lay perfectly still in a small space for a relatively long timespan. They are less restricted, making it possible for essentially every motivated individual that fits the inclusion criteria to participate in an EEG-study.

2.3. Limitations of EEG

The coarse spatial resolution of EEG makes it challenging to identify exact locations of neural sources and discriminate neural sources that are spatially close. An important reason is the scattering of neural signals by tissue between the cortex and the electrodes, such as the meningeal layers and the skull (Nunez & Srinivasan, 2006b). Important is the 'inverse problem': despite so-called 'source localisation approaches', we cannot deduce the exact pattern of brain activations based on the observed EEG data, as many different patterns can give rise to the same EEG responses (Buxton, 2009). Therefore, the signal measured by an EEG-electrode reflects a relatively large, non-specific brain area, in the order of several centimetres (Teplan, 2002).

Another limitation of EEG is that the recorded data is restricted to cortical signals. Consequently, it is impossible to record data from subcortical regions such as the amygdala with scalp-EEG. Instead, intracranial EEG is performed using intracerebral electrodes. These studies are performed in individuals with epilepsy who are eligible for surgery, as intracranial EEG is used to determine the epileptic focus (Lachaux et al., 2003).

2.4. Pre-processing of EEG data

First, data is quality checked for possible artefacts and other anomalies. Then, data is cropped into segments containing one sequence (i.e., pieces of the time course containing data that belongs to one condition). Next, a bandpass filter is applied to exclude irrelevant high and low frequency information. In a next step, the data is down sampled, from a sampling rate of 512 Hz during acquisition to 256 Hz to analyse the data, reducing the workload on the computer while keeping sufficient data points. If necessary, the data of noisy or defective electrodes is re-estimated by interpolating the three spatially nearest electrodes. In addition, in participants that blink more than two standard deviations above

average, a correction for eye-blinking is applied using independent component analysis (ICA). All segments are then re-referenced to a common average reference, for which we use the average of all active electrodes. Finally, the segments are cropped to only contain relevant data (without the data during fade-in and fade-out).

2.5. Fast periodic visual stimulation frequency-tagging EEG

Classically, an event-related potentials (ERP) approach is used, studying the EEG-signal in response to particular events in the time-domain. However, these recordings often take a long time due to the low signal-to-noise ratio of this approach. Furthermore, subjective choices are made throughout the analysis (e.g., selecting time windows and determining ERP components). For that reason, we used fast periodic visual stimulation (FPVS) in combination with frequency-tagging EEG: a more sensitive approach entailing implicit measures to capture automatic neural processes.

Frequency-tagging EEG depends on the synchronisation of brain activation to a periodically flickering stimulus (Adrian & Matthews, 1934; Norcia et al., 2015). To study this, we must transform the raw data (i.e., EEG signal in the time domain) to the frequency domain using a fast Fourier transformation, a so-called 'spectral decomposition'. This results in a frequency domain representation, revealing the required amplitude for every frequency to reconstruct the original waveform. After transforming the data from the time domain into the frequency domain, we can see a response at exactly the frequency at which the flickering stimulus was presented (Figure 1.7), as the amplitude at this frequency exceeds the amplitudes at neighbouring frequencies. For instance, when six stimuli are presented every second (i.e., at a rate of 6 Hz), we expect to find a response at the tagged frequency of 6 Hz. Moreover, we can study whether our brains are sensitive to a specific kind of stimulus among other stimuli, by presenting an "oddball stimulus" among the "base stimuli" in a periodic manner (e.g., every fifth stimulus: 6 Hz/5 = 1.2 Hz). If our brains automatically process the oddball stimulus as being different than the base stimulus, this will show up as a response at the 1.2 Hz frequency tag in the frequency domain. In Chapter 5, we use this analysis to study the neural sensitivity to facial identities and expressions in individuals with and without ASD.

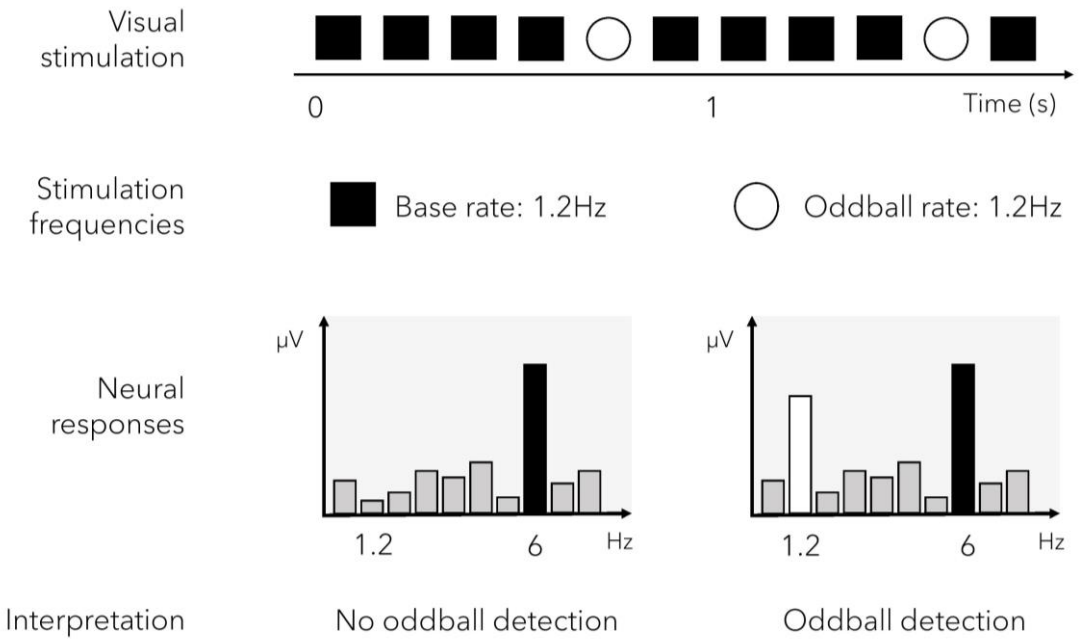


Figure 1.7. Fast periodic visual stimulation combined with frequency-tagging EEG. Activity in the brain synchronises to the frequency at which visual stimulation is presented. The upper row shows the visual stimulation: base images (black squares) are presented at a base rate frequency of 6 Hz, periodically interleaved by oddball images (white circles) presented at an oddball frequency of 1.2 Hz. On the graphs, neural responses are shown. If participants' brains fail to detect oddball images in a stream of base images, we only see a general base rate response at 6 Hz (left graph). In contrast, if participants can detect the oddball images in a stream of base images, we see a response at the oddball frequency of 1.2 Hz in addition to the general base rate response at 6 Hz (right graph).

Chapter 2

The effect of spatial smoothing

Abstract

Spatial smoothing is often used when pre-processing neuroimaging data. There are several reasons for including this pre-processing step, among which a desirable increase of the signal-to-noise ratio. Notwithstanding, many reported multi-voxel pattern analyses are performed on unsmoothed data. The goal of this study was to investigate the effect of spatial smoothing on MVPA results, by using a simple motor paradigm.

We acquired functional magnetic resonance imaging (fMRI) data of eight participants. Participants were instructed to press four buttons with the middle- and index fingers of both hands based on auditory commands. When analysing the data, seven levels of smoothing were used (kernels ranged from 0-15mm FWHM). We studied the effect of spatial smoothing in the motor cortex, the prefrontal cortex, the low-level auditory cortex, and the high-level auditory cortex using correlational MVPA. In addition, different conditions entailing different spatial scales (same-finger, same-hand, different-hand) were compared.

Overall, independent of the degree of smoothing, correlational MVPA showed distinctive patterns for the different hands in all studied regions of interest (motor cortex, prefrontal cortex, and auditory cortices). Regarding the effect of smoothing, our findings suggest that results from correlational MVPA show a minor sensitivity to smoothing. Moderate amounts of smoothing (in this case, 1–4 times the voxel size) improved MVPA correlations, from a slight improvement to large improvements depending on the region involved. None of the regions showed signs of a detrimental effect of moderate levels of smoothing. Even higher amounts of smoothing sometimes had a positive effect, most clearly in the low-level auditory cortex. We conclude that smoothing seems to affect MVPA results. Researchers should therefore be mindful about the choices they make.

This chapter is a slightly adapted version of the article published as:

Hendriks, M. H. A., Daniels, N., Pegado, F., & Op de Beeck, H. P. (2017). The effect of spatial smoothing on representational similarity in a simple motor paradigm. *Frontiers in Neurology, 8, 222*. https://doi.org/10.3389/fneur.2017.00222

1. Introduction

Spatial smoothing is part of the pre-processing of functional magnetic resonance imaging (fMRI) data and is most often performed using a three-dimensional Gaussian filter ('kernel') of several millimetres to filter the image. In this way, high-frequency information is removed, while low-frequency information remains (Poldrack et al., 2011). Although the choice of a smoothing level appears to be arbitrary, it might not be without consequence. It is one of several parameters that are often set 'by default' but might nevertheless influence the outcome of statistical analyses (Poldrack et al., 2011).

1.1. Reasons to smooth neuroimaging data

Smoothing is incorporated in the analysis of neuroimaging data for several reasons. A first, and extensive, argument is a matter of spatial resolution inherent to the method of fMRI. Blood oxygen level dependent (BOLD) fMRI localises changes in oxygenation levels in the blood that are related to synaptic activation (Logothetis, 2008). Hence, BOLD fMRI indirectly measures brain activity through a haemodynamic signal that is also spatially smoothed. The smallest unit of measurement used in fMRI, a voxel, still contains a myriad of neurons. In addition, the vascular response measured using fMRI expands over various millimetres, partially resulting from 'draining veins' that remove oxygen-rich blood from the active voxels (Lindquist & Wager, 2016). This causes the point spread function (PSF) of the neural response to be spatially widened, which in turn results in weaker precision and thus a smaller resolution (Parkes et al., 2005). This first argument shows the biggest limitations of fMRI as a method. Smoothing is therefore used to increase the signal-to-noise ratio for the larger-scale information that is relevant in most fMRI studies (Poldrack et al., 2011). A second reason to smooth is related to its beneficial effect for the validity of statistical assumptions as incorporated in the well-known Random Field Theory (Friston, 2003). Finally, inter-individual differences in anatomy must be considered when analysing fMRI data. As such, spatial smoothing helps to overcome the inter-individual differences in anatomy (Friston, 2003).

1.2. Multi-voxel pattern analysis

Despite the abundant use of spatial smoothing in fMRI research in general, it is much less commonly used in one specific type of fMRI analysis, namely multi-voxel pattern analysis (MVPA). MVPA focuses upon patterns of activity across voxels instead of single-voxel activations (Haxby et al., 2001). There are many types of MVPA, but our focus will be on the type used in this report: correlational MVPA. Correlational MVPA entails a split of data in two subsets, followed by a correlation between the neural activity patterns for conditions in one subset of the data with the patterns of conditions in the other subset (Op de Beeck et al., 2006; Op de Beeck, 2010). This has also been referred to as representational similarity analysis (Kriegeskorte et al., 2008). By comparing the correlation between same conditions with the correlation between different conditions, we can find out whether the neural patterns contain any information about the different conditions. If the correlation between same conditions is reliably higher, this means that the patterns of brain activation provide reliable information about which condition was presented (Haxby et al., 2001).

1.3. Scale of information

Op de Beeck (2010) studied the sensitivity of MVPA results to different levels of smoothing in the visual cortex. The motive for this study was the suggestion of so-called hyperacuity. Several authors suggested that MVPA can be used to pick up brain maps that are organised at a scale that is finer than the voxel size, such as picking up the signals from orientation columns at a sub-millimetre scale through voxels of 3 mm isotropic (Downing et al., 2007; Kamitani & Tong, 2005). The authors did not perform spatial smoothing on their data, and indeed reported findings that suggest hyperacuity. However, Op de Beeck (2010) showed that the outcome of MVPA is surprisingly robust to the level of spatial smoothing. More specifically, highly smoothed data contained at least a similar amount of information as unsmoothed data. When using correlational MVPA, larger amounts of smoothing even increased the correlations. Hence, picking up on small-scale activation patterns using MVPA seems impossible. An intense debate has unfolded since, about the degree to which MVPA results are driven by small- or large-scale selectivity maps (in favor of small-scale or multiple-scale selectivity maps: Alink et al., 2013; Clifford et al., 2011; Clifford & Mannion, 2015; Mannion et al., 2009; Swisher & Tong, 2012; in favor of large-scale selectivity maps: Carlson, 2014; Freeman et al., 2011, 2013).

More in detail, several mechanisms have been suggested to account for the findings that support hyperacuity (Chaimow et al., 2011). A first hypothesised mechanism involves local, irregular, and arbitrary deviations in the functional organisation of the brain at a columnar level, which can cause biases at the level of voxels, which can be picked up when performing MVPA (Haynes & Rees, 2006; Kamitani & Tong, 2005; Kriegeskorte & Bandettini, 2007). Each voxel contains columns with different orientation preferences. Importantly, a bias arises because these preferences are distributed unevenly across voxels. The authors found evidence for a contribution of low frequency as well as high frequency components underlying these random variations. Secondly, draining veins are expected to play a role, as voxels can include signals from larger blood vessels, causing a bias in decoding (Kamitani & Tong, 2005; Kriegeskorte & Bandettini, 2007). A third mechanism was proposed by Kriegeskorte and colleagues (2010). In their model, fMRI voxels are believed to act like spatiotemporal filters of neural activity, as every voxel samples from a unique structure of blood vessels. For full explanations of the aforementioned (and other) proposed mechanisms, we refer to the article of Chaimow et al., 2011.

Finally, Sengupta and colleagues (2017) studied the effect of the acquisition resolution in V1 on the decoding of orientation. They suggest that the opposing views are not mutually exclusive, namely the idea that fMRI data 'is broadband in nature' and contains both small-scale and large-scale activation patterns.

1.4. Spatial organisation

Investigating the effect of smoothing can also provide information about the spatial organisation of neural representations. To give just one example, Brants and colleagues (2011) used a manipulation of spatial smoothing to study the spatial organisation of the ventral occipitotemporal cortex. They used correlational MVPA and found that correlations were higher when data were smoothed compared to non-smoothed data. Additionally, they examined whether this effect of smoothing was the same for all spatial scales, in this case contrasting conditions that are differentiated at the subordinate level (baby-face and elderly face, small spatial scale) or different categories (faces and houses, large spatial scale). They found an interaction effect in which the correlation increased less for the subordinate distinctions, suggesting that the selectivity maps related to these subordinate distinctions are organised at a finer spatial scale.

1.5. Current study

Up to now, these studies focused exclusively upon the visual cortex. Here, we explored the effect of spatial smoothing on MVPA results in other brain regions using a non-visual paradigm. In particular, we studied this effect in the motor cortex, the prefrontal cortex, the low-level auditory cortex (A1) and the high-level auditory cortex (A2). For this purpose, a fairly basic motor paradigm with auditory instructions was used.

The first goal encompassed studying the sensitivity of MVPA results to the level of smoothing. For this purpose, we used seven levels of smoothing (ranging from no smoothing to 15mm FWHM in steps of 2.5mm) and compared the results. A second goal was to investigate the extent to which smoothing would affect results with different spatial scales. For this reason, we included conditions that were expected to activate nearby parts of the motor cortex (such as different fingers of the same hand) as well as conditions that should activate far-away parts of the motor cortex in different hemispheres (such as fingers of a different hand). Based on previous findings, we predicted that a larger amount of smoothing would increase the difference in correlations between same and different conditions, predominantly for the largest spatial scale.

2. Materials and Methods

2.1. Participants

Data were acquired using eight neurotypical subjects (six female; mean age of 22.75 years with a standard deviation of 3.06; one left-handed). All participants reported absence of neurological or psychiatric history. This study was carried out in accordance with the recommendations of the medical ethics committee of the KU Leuven with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The study served as a control experiment in a more extensive study, of which the protocol was approved by the medical ethics committee of the KU Leuven.

2.2. Stimuli and fMRI task

Auditory stimuli were recorded to serve as instructions. The spoken words 'left middle finger', 'left index finger', 'right index finger' and 'right middle finger' were used in so-called Finger runs. Spoken words 'one', 'two', 'three' and 'four' were used in so-called Number runs. Stimuli were recorded by one male and one female voice and were in Dutch.

Brain imaging data were collected while participants received the spoken instructions to press one of four buttons. Buttons were pressed using middle- and index fingers of both hands. There were thus four conditions, one for each finger. One run lasted for 504 seconds and consisted of 112 events of 4.5 s, 96 of which were experimental events with stimulus presentation. Visually, each trial started with a blank screen presented for 2.5 s, followed by a screen with a fixation cross for 2 s (Figure 2.1). Although visual stimulation was not strictly necessary to complete the task, black screens and fixation crosses were used to ensure equal visual input for all participants throughout the experiment. The auditory cues were presented while the blank screen was shown. The experiment comprised four runs per participant; two 'Finger'- and two 'Number'-runs in randomised order. In each run, 202 volumes were acquired, starting approximately five seconds before stimulus/fixation presentation, and ending approximately five seconds after stimulus/fixation presentation ended.

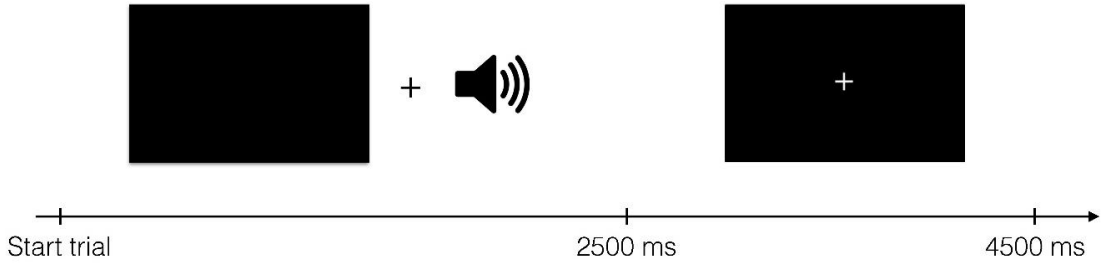


Figure 2.1. Structure of one trial. During auditory stimulus presentation, a black screen was shown. The auditory stimulus started 600ms after the black screen appeared. After 2.5 s, a fixation cross was shown for 2 s. Each trial lasted a total of 4.5 s.

2.3. fMRI data acquisition

Data were acquired using a 3T Philips Ingenia CX scanner (Department of Radiology of KU Leuven). A 32-channel head coil was used. Functional data consisted of T2*-weighted echoplanar images (EPIs) with voxel size 2.52 x 2.58 x 2.5mm, an interslice gap of 0.2mm on top of the slice thickness of 2.5mm, repetition time 2550 ms, echo time 30 ms, acquisition matrix 84 x 82 voxels, 45 slices per volume acquired in ascending order, and a field of view (FOV) of 211mm x 211mm x 121mm. Additionally, a high-resolution T1-weighted anatomical scan was acquired with voxel size of 0.98 x 0.98 x 1.2 mm, repetition time 9.6 ms, echo time 4.6 ms, acquisition matrix 256 x 256 voxels, and 182 slices. Stimuli were presented using Psychtoolbox 3 (Brainard, 1997). Visual stimuli were projected on a screen using an NEC projector with a NP21LP lamp. The participant viewed the screen through a mirror attached to the head coil. Viewing distance was approximately 64 cm. Auditory stimuli were presented via headphones. Before starting, participants were asked to indicate whether the volume was of an acceptable level, to make sure they could easily understand the instructions.

2.4. fMRI data-analysis

Data were analysed using two different approaches. A first approach followed the most frequently used pipeline of fMRI data analysis, in which smoothing is performed as a step during pre-processing. In the second approach, smoothing was performed after defining the general linear model, on anatomically masked beta-images.

2.4.1. Approach 1: smoothing during pre-processing

2.4.1.1. Pre-processing.

Data were processed using the Statistical Parametric Mapping software package (SPM8, Wellcome Department of Cognitive Neurology, London, UK) and custom MATLAB code (Mathworks, Inc.). Pre-processing involved correction of the functional images for slice timing differences and realignment with the mean image to correct for head motion. Functional and anatomical images were then co-registered, using the mean realigned image as reference image, and normalised to the MNI template.

2.4.1.2. Smoothing

In a final step of the pre-processing, normalised functional images were smoothed using Gaussian kernels with different full width at half maxima (FWHM). The FWHM is related to standard deviation (2.55 times the standard deviation, Poldrack et al., 2011). In line with the goal of this writing, the data were analysed using seven levels of smoothing ranging from no smoothing to a kernel of 15x15x15mm (approximately six times the original voxel size), in steps of 2.5mm (approximately the voxel size). The pre-processed data were used in further analyses.

2.4.1.3. General Linear Model

We modelled the onset of each trial by an event with a duration of 400 ms centred around each subject's finger movement to capture the signal in the motor cortex. This choice was made a priori, without further detailed analyses. The finger movements were operationalised individually for every participant and every trial. The neural signal was modelled individually for every subject using a general linear model (GLM). This model was generated for each of the four runs and contained four regressors of interest (one for each stimulus condition, being four fingers) and six additional regressors to account for head motion (realignment parameters obtained during motion correction). After fitting the general linear model, the parameter estimates were used to calculate each voxel's response during each of the four conditions. This resulted in so-called 'beta' values, which were used to perform MVPA.

2.4.1.4. Definition of regions of interest

We examined whether movement of different fingers can be distinguished based on neural activation patterns. We focused primarily on the motor cortex. In addition, we also included the prefrontal cortex, and low- and high-level auditory cortices. Voxels were first selected based on a whole-brain univariate contrast of all four conditions minus baseline. We used a threshold of $p < 0.001$ (uncorrected for multiple comparisons). Voxels that were significantly activated by this contrast were selected for each participant. This selection was further restricted anatomically, by selecting those voxels that were conjointly present in the previous selection and anatomical masks of all studied regions. The anatomical masks were created with the anatomical WFU PickAtlas Toolbox (Wake Forrest University PickAtlas, http://fmri.wfubmc.edu/cms/software). The motor cortex was defined by Brodmann areas BA 4 (primary motor cortex) and 6 (premotor cortex) and contained 8120 voxels. The prefrontal cortex was specified by the frontal lobe minus BA 4 and 6, which included 65021 voxels. The low-level auditory cortex included BA 41 and 42 and comprised 762 voxels. The high-level auditory cortex was defined by BA 22 and consisted of 1820 voxels.

2.4.1.5. Correlational MVPA

Data of every voxel within a region of interest was normalised for every run by cocktail blank subtraction of the mean response across all conditions (Haxby et al., 2001; Op de Beeck et al., 2008). The data were then divided by randomly assigning the runs into two halves. We computed pairwise correlations between multi-voxel patterns of same and different fingers. This yielded a 4x4 correlation matrix (Figure 2.2). In this matrix, diagonal cells (white) show the correlation of a condition with itself, while non-diagonal cells (blue) show the correlation between different conditions. We computed the mean diagonal and the mean non-diagonal values of this matrix for every subject, as well as the difference between these averages (diagonal minus non-diagonal). When this difference is significantly higher than zero across subjects, we can infer that the multi-voxel patterns in a brain region contain information to distinguish between different conditions (i.e., different fingers). We studied the effect of smoothing on the results of this multi-voxel pattern analysis.

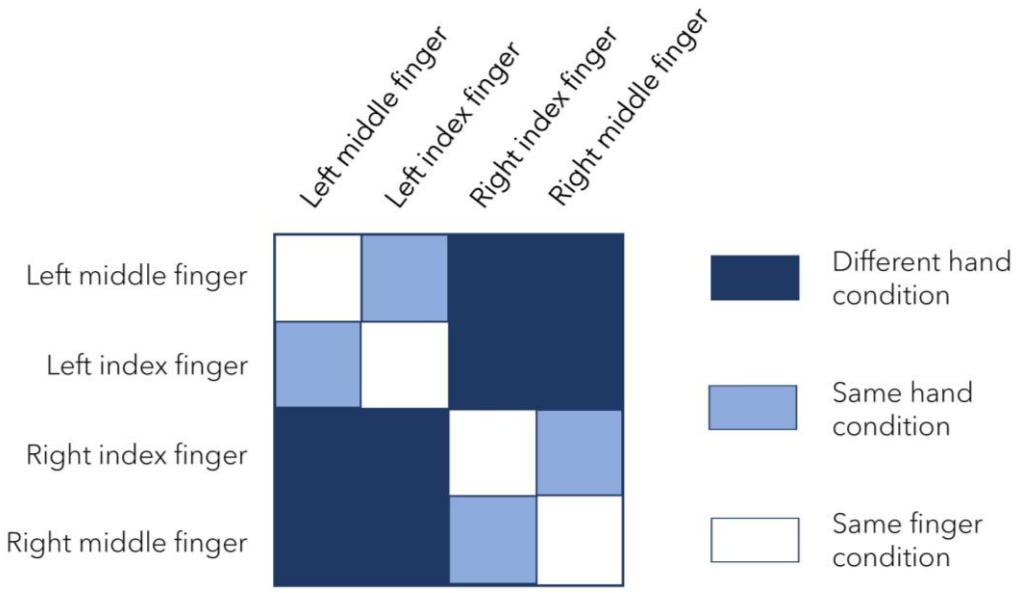


Figure 2.2. Representation of conditions. Same-fingers condition (white) entails correlations between same fingers. The same-hand condition (light blue) entails correlations between different fingers on the same hand. Finally, the different-hand condition (dark blue) entails correlations between fingers on different hands. In addition, the model used to analyse the data can be derived from this image. Diagonal (white) entails a correlation of neural activity for movement of the same fingers. On the non-diagonal (blue), cells contain a correlation between neural activation for movement of different fingers.

2.4.1.6. Spatial organisation

Spatial scale was operationalised by different conditions (Figure 2.2): we looked at the correlation of one finger with the same finger (diagonal, same-finger condition), the correlation between different fingers on the same hand (non-diagonal, light blue, same-hand condition), and the correlation between fingers on different hands (non-diagonal, dark blue, different-hand condition). We studied how smoothing affects MVPA results while considering different spatial scales. We expected to find that the correlation between same fingers would be higher than the correlation between different fingers on the same hand, which in turn would be higher than the correlation between different fingers on different hands. This was operationalised by computing pairwise differences in mean correlations and studying their significance. We also studied whether there was an interaction between spatial scale and smoothing.

2.4.2. Approach 2: Smoothing after masking ROIs

2.4.2.1. Pre-processing

Except for the smoothing in approach 1, data were processed in the same way. In approach 2, there was no smoothing during pre-processing.

2.4.2.2. General Linear Model

We modelled the GLM in the same way as above, with one exception: the input data. Here the input data were the unsmoothed pre-processed data.

2.4.2.3. Masking of beta-images

This step is unique to the second approach. We created purely anatomical masks with the anatomical WFU PickAtlas Toolbox (Wake Forrest University PickAtlas, http://fmri.wfubmc.edu/cms/software) as outlined above (2.4.1.4. Definition of regions of interest). These anatomical masks were used to isolate the information within the regions of interest and ignore the information outside these regions by treating these values as missing values (Alink et al., 2013).

2.4.2.4. Smoothing

Smoothing was performed on the masked beta-images. Equal to the first approach, data were smoothed using Gaussian kernels with FWHM ranging from no smoothing to a kernel of 15x15x15 mm in steps of 2.5 mm.

2.4.2.5. Definition of regions of interest

Regions of interest were defined identically to the procedure for the first approach.

2.4.2.6. Correlational MVPA

The multivariate analysis was performed in the same way as for the first approach.

2.4.2.7. Spatial organisation

The spatial scales were examined in the exact same manner as for the first approach.

3. Results

3.1. Approach 1: Smoothing during pre-processing

3.1.1. Effect of smoothing

To study the effect of smoothing on MVPA results, we first compared the mean correlations on the diagonal to the mean correlations on the non-diagonal and found that this difference was significantly higher than zero for every level of smoothing in every region, except 2.5 mm FWHM in the high-level auditory cortex (Figure 2.3) (t-test across subjects with a Bonferroni corrected alpha-level of 0.0071 (0.05/7) per region; motor cortex: $t(7) > 4.9726$, $p < 0.0016$ for all levels of smoothing; prefrontal cortex: $t(7) > 6.5413$, $p < 0.0003$ for all levels of smoothing; low-level auditory cortex: $t(7) > 3.8823$, $p < 0.006$ for all levels of smoothing; high-level auditory cortex: $t(7) > 3.7435$, $p < 0.0072$ for all levels of smoothing).

In addition, we examined whether the comparison between diagonal and non-diagonal was affected by smoothing within each region. When inspecting the graphs, we can see a positive trend: the difference between diagonal and non-diagonal seems to increase with a higher level of smoothing. This trend remained in a few regions up to the highest level of smoothing. Statistically speaking, we only found a main effect of smoothing in the low-level auditory cortex, not in the three other areas (one-way ANOVA per region; motor cortex: $F(6,49) = 0.09$, $p = 0.9974$; prefrontal cortex: $F(6,49) = 0.5$, $p = 0.805$; low-level auditory cortex: $F(6,49) = 5.81$, $p = 0.0001$; high-level auditory cortex: $F(6,49) = 1.05$, $p = 0.4078$).

In a last step, we performed a two-way ANOVA with factors smoothing and brain region to test the presence of an interaction between amount of smoothing and brain region. We found a main effect of brain region ($F(3,196) = 55.86$, $p < 0.0001$), a main effect of smoothing ($F(7,196) = 3$, $p = 0.0079$), but no interaction ($F(18,196) = 0.18$, $p < 0.981$).

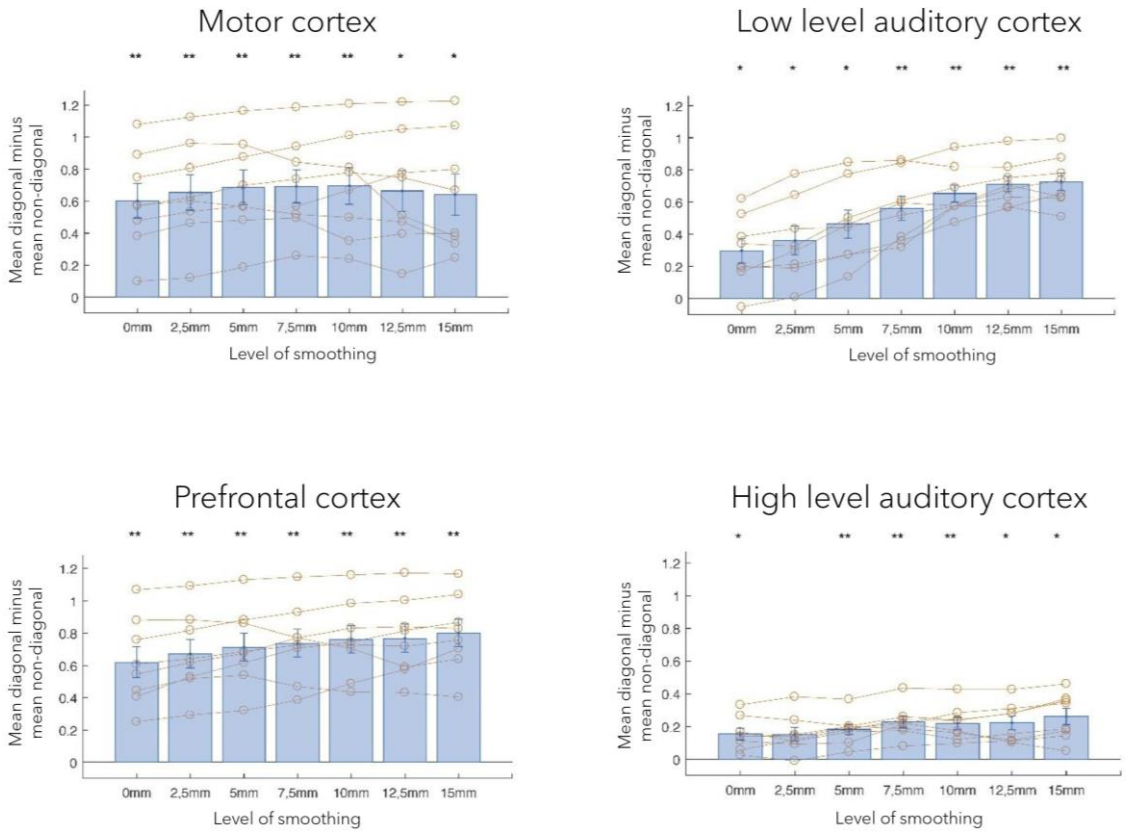


Figure 2.3. Differences between mean diagonal and mean non-diagonal for different levels of smoothing in the four regions of interest using **approach 1**: smoothing as part of pre-processing. * $p < 0.0071$ (Bonferroni corrected: 0.05/7), ** $p < 0.001$. Error bars represent standard errors of the mean. Lines show data points for individual subjects.

3.1.2. Smoothing and spatial scales

Next, we studied whether smoothing affects MVPA results in a different way when looking at different spatial scales. We computed the mean correlation for every condition in all regions and investigated the difference in correlation between conditions for every level of smoothing for every subject (Figure 2.4). On these data, we applied a two-way ANOVA per region and found a main effect of condition in each region (motor cortex: $F(2,147) = 522.34$, $p < 0.0001$; prefrontal cortex: $F(2,147) = 1002.71$, $p < 0.0001$; low-level auditory cortex: $F(2,147) = 316.48$, $p < 0.0001$; high-level auditory cortex: $F(2,147) = 68.95$, $p < 0.0001$), a main effect of smoothing in motor and prefrontal cortices (motor cortex: $F(6,147) = 3.06$, $p = 0.0076$; prefrontal cortex: $F(6,147) = 3.31$, $p = 0.0044$) but not low-level and high-level auditory cortices (low-level auditory cortex: $F(6,147) = 1.62$, $p = 0.1452$; high-

level auditory cortex: F(6,147) = 0.85, p = 0.5331), and an interaction effect in each region (motor cortex: F(12,147) = 12.7, p < 0.0001; prefrontal cortex: F(12,147) = 13.98, p < 0.0001; low-level auditory cortex : F(12,147) = 7.27, p < 0.0001; high-level auditory cortex: F(12,147) = 8.34, p < 0.0001).

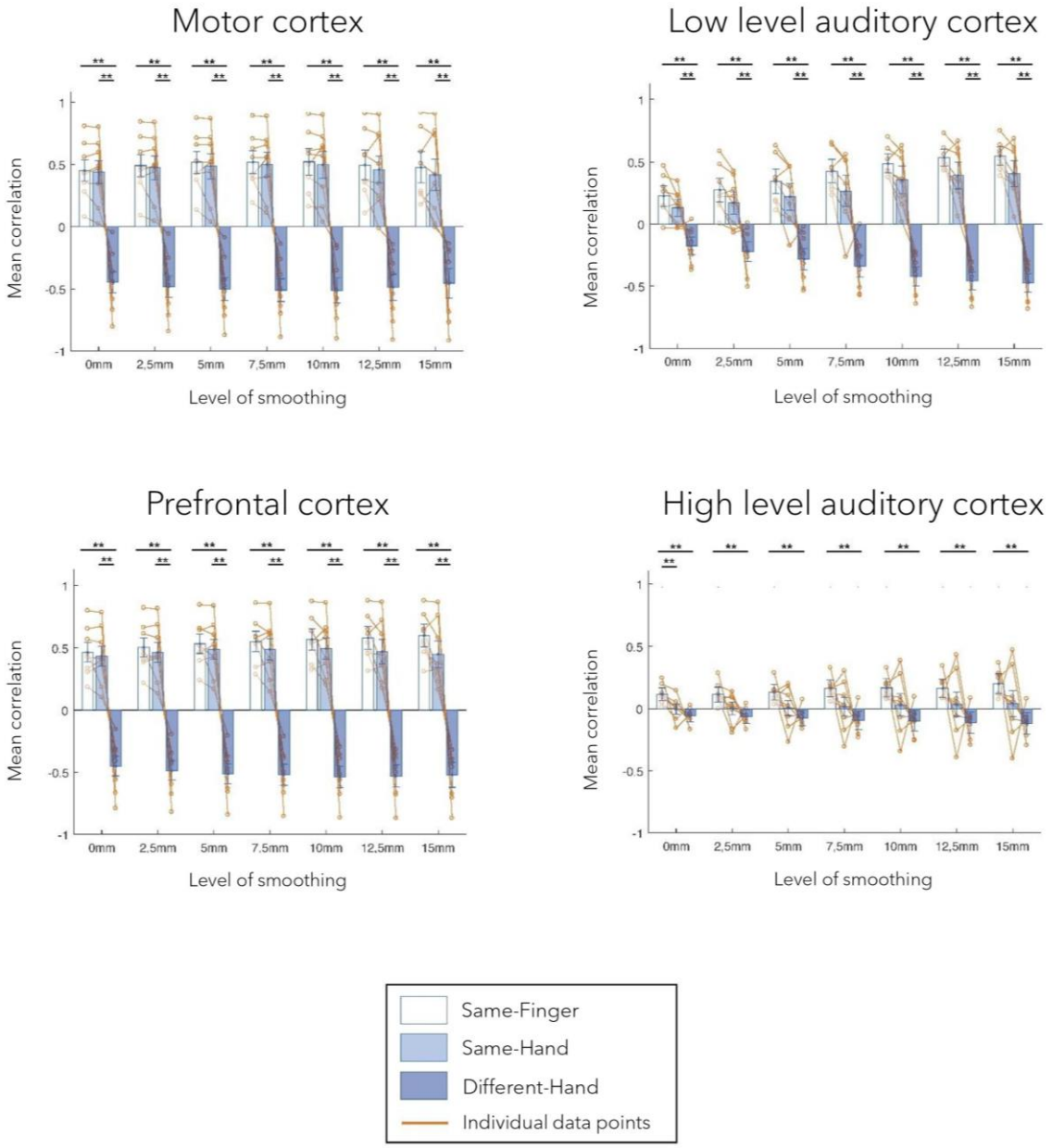


Figure 2.4. Comparisons between different conditions for distinct smoothing levels in all studied regions of interest using the **first approach**: smoothing as part of pre-processing. * p < 0.0024 (Bonferroni corrected: 0.05/21), ** p < 0.001. Error bars represent standard errors of the mean, lines and dots represent data points of individual subjects.

In addition, we examined the results across conditions per region, using a Bonferroni corrected p-value of 0.0024 (0.05/21). There were clear similarities between the patterns in the motor cortex, the prefrontal cortex, and the low-level auditory cortex. Namely, we found no significant differences between the same-finger and the same-hand conditions ($t(62) < 2.2751$, $p > 0.0264$ in all cases), but a significant difference between same-finger and different-hand conditions ($t(94) > 8.7428$, $p < 0.0001$ in all cases), and the same-hand and different-hand conditions ($t(94) > 7.1889$, $p < 0.0001$ in all cases). On the other hand, in the high-level auditory cortex, we only found a consistent significant difference between the same-finger and different-hand conditions ($t(94) >$, $p < 0.0001$), and between the same-finger and same-hand without smoothing conditions ($t(62) = 3.6373$, $p < 0.0001$). However, we did not find a significant difference between the same-hand and different-hand conditions ($t(94) < 2.7948$, $p > 0.0063$ in all cases).

3.2. Approach 2: Smoothing after masking ROIs

3.2.1. Effect of smoothing

Identically to the first approach, we compared the mean correlations on the diagonal to the mean correlations on the non-diagonal and found that this difference was significantly higher than zero for every level of smoothing in every region, except 2,5 and 5 mm FWHM in the low-level auditory cortex, and 2,5 mm FWHM in the high-level auditory cortex (Figure 2.5) (t-test across subjects with a Bonferroni corrected alpha-level of 0.0071 (0.05/7) per region; motor cortex: $t(7)> 3.7547$, $p < 0.0071$ for all levels of smoothing; prefrontal cortex: $t(7) > 6.5413$, $p < 0.0003$ for all levels of smoothing; low-level auditory cortex: $t(7) > 3.3961$, $p < 0.0115$ for all levels of smoothing; high-level auditory cortex: $t(7) > 3.7071$, $p < 0.0076$ for all levels of smoothing).

In addition, we again examined whether the comparison between diagonal and non-diagonal was affected by smoothing within each region. When inspecting the graphs, we again see a positive trend: the difference between diagonal and non-diagonal seems to increase with a higher level of smoothing. In contrast, as for the first approach, we only found a main effect of smoothing in the low-level auditory cortex, not in the three other areas (one-way ANOVA per region; motor cortex: $F(6,49) = 0.12$, $p = 0.9931$; prefrontal cortex: $F(6,49) = 0.51$, $p = 0.7997$; low-level auditory cortex: $F(6,49) = 3.96$, $p = 0.0026$; high-level auditory cortex: $F(6,49) = 1.86$, $p = 0.1076$).

In a last step, we again performed a two-way ANOVA to test the presence of an interaction between amount of smoothing and brain region. We found a main effect of brain region ($F(3,196) = 34.96$, $p < 0.0001$), a main effect of smoothing ($F(7,196) = 2.67$, $p = 0.0163$), but no interaction ($F(18,196) = 0.78$, $p < 0.7173$).

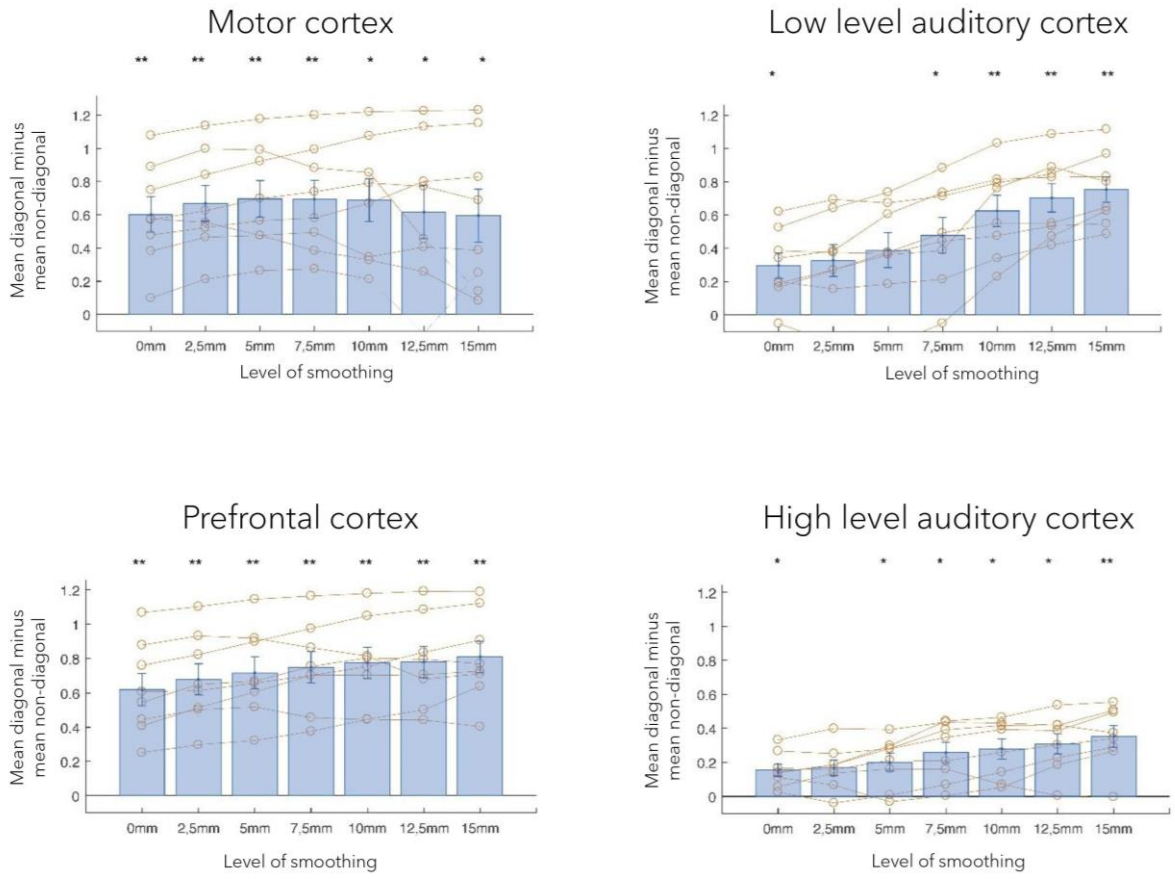


Figure 2.5. Differences between mean diagonal and mean non-diagonal for different levels of smoothing in the four regions of interest using **approach 2**: smoothing after masking of beta-images. * $p < 0.0071$ (Bonferroni corrected: 0.05/7), ** $p < 0.001$. Error bars represent standard errors of the mean. Lines show data points for individual subjects.

3.2.2. Smoothing and spatial scales

We also studied whether smoothing affects MVPA results in a different way when looking at different spatial scales in approach 2. We computed the mean correlation for every condition in all regions and investigated the difference in correlation between conditions for every level of smoothing for every subject (Figure 2.6). On these data, we applied a two-way ANOVA per region and found a main effect of condition in each region (motor cortex: $F(2,147) = 501.63$, $p < 0.0001$; prefrontal cortex: $F(2,147) = 1261.64$, $p < 0.0001$; low-level auditory cortex: $F(2,147) = 213.49$, $p < 0.0001$; high-level auditory cortex: $F(2,147) = 79.25$, $p < 0.0001$), a main effect of smoothing in motor and prefrontal cortices (motor cortex: $F(6,147) = 3.04$, $p = 0.0078$; prefrontal cortex: $F(6,147) = 4.17$, $p = 0.0007$) but not low-level and high-level auditory cortices (low-level auditory cortex: $F(6,147) = 1.25$, $p = 0.2852$; high-level auditory cortex: $F(6,147) = 1.73$, $p = 0.1184$), and an interaction effect in each region (motor cortex: $F(12,147) = 13.2$, $p < 0.0001$; prefrontal cortex: $F(12,147) = 16.48$, $p < 0.0001$; low-level auditory cortex: $F(12,147) = 5.85$, $p < 0.0001$; high-level auditory cortex: $F(12,147) = 8.73$, $p < 0.0001$).

Furthermore, we examined the results across conditions per region, using a Bonferroni corrected p-value of 0.0024 (0.05/21). Even more so than for the first approach, there were clear similarities between the patterns in the motor cortex, the prefrontal cortex, and the low-level auditory cortex. Namely, we found no significant differences between the same-finger and the same-hand conditions ($t(62) < 1.7469$, $p > 0.0856$ in all cases), but a significant difference between same-finger and different-hand conditions ($t(94) > 8.3309$, $p < 0.0001$ in all cases), and the same-hand and different-hand conditions ($t(94) > 7.0811$, $p < 0.0001$ in all cases). In the high-level auditory cortex, we also found a consistent significant difference between the same-finger and different-hand conditions ($t(94) > 5.0441$, $p < 0.0001$). However, the difference between the same-hand and different-hand condition was only significant in the four biggest levels of smoothing ($t(94) > 3.2512$, $p < 0.0016$ in all significant cases), and the difference between the same-finger and same-hand conditions was only significant for results without smoothing and with smoothing of 2,5 mm FWHM ($t(62) = 3.2404$, $p < 0.0019$ for the two significant cases).

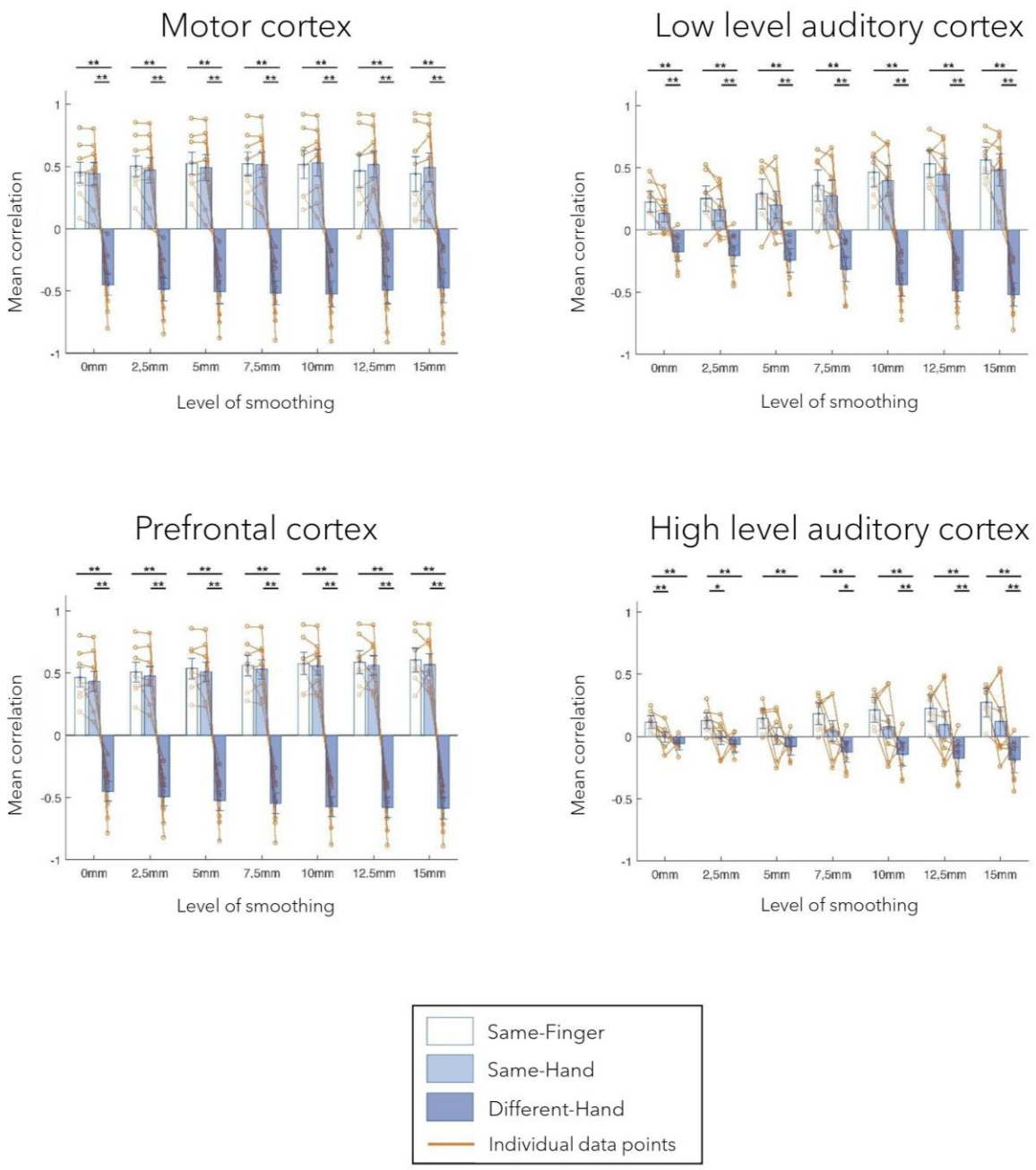


Figure 2.6. Comparisons between different conditions for distinct smoothing levels in all studied regions of interest using the **second approach**: smoothing after masking of beta-images. * $p < 0.0024$ (Bonferroni corrected: 0.05/21), ** $p < 0.001$. Error bars represent standard errors of the mean, lines and dots represent data points of individual subjects.

4. Discussion

4.1. Effect of smoothing

We studied the effect of spatial smoothing on the results of correlational MVPA. We expected correlations to be higher between patterns of the same condition, than between patterns of different conditions. In other words, we expected the diagonal cells of the correlation matrices to contain higher values than the non-diagonal cells (Figure 2.2). As expected, we found that the difference between diagonal and non-diagonal was significant in almost all smoothing levels in almost all studied regions, in both approaches. We can thus reliably distinguish activity from conditions differing in motor and auditory dimensions based on neural data with almost all smoothing levels in all studied regions in both approaches. Across all regions, there was an overall positive effect of smoothing. In the motor cortex, our results show a different pattern than the other three regions, namely a decrease of information for the highest levels of smoothing (i.e., 12.5 and 15 mm FWHM). In the other three regions, and most obviously the low-level auditory cortex, smoothing even with the largest kernel did not hurt MVPA results and if anything seemed to have a slight positive effect. To summarise, smoothing does not seem to degrade the results of correlational MVPA in this combined motor/auditory paradigm.

Our results seem to be largely in line with the findings of Op de Beeck (2010). He found that the effect size of correlational MVPA was higher when using smoothing compared to no smoothing in the primary visual and lateral occipital cortex. In addition, a parallel decoding MVPA approach showed that relatively large amounts of spatial smoothing do not hurt results of decoding MVPA. In contrast, note that some studies have shown that larger amounts of smoothing induce a decrease in decoding accuracy (Misaki et al., 2013; Swisher et al., 2010).

There are various possible explanations for the effect of smoothing on MVPA results. Chaimow and colleagues (2011) explained several mechanisms, as mentioned in the introduction. The fact that results of (correlational) MVPA are fairly robust to smoothing, is at face value an argument against hyperacuity (Op de Beeck, 2010). Sengupta and colleagues (2017) speculate about the Nyquist criterion: with a particular sampling frequency we can only measure frequencies up to half the sampling frequency. In this case, it would mean that with a voxel size of 2.5 mm we could measure frequencies up to 5 mm.

In all regions, the signal clearly increased up to 5mm smoothing (and further), so it seems possible that this criterion plays a role. However, we cannot exclude other explanations, like draining veins or local, random variations in the brain's functional organisation. Furthermore, besides the effect of smoothing, we noticed clear differences between the regions of interest regarding the overall trend visible in the figures. An obvious explanation for regional differences could be the size of the region, operationalised by the number of voxels. However, only the prefrontal cortex mask is a lot bigger than the other three, hence this does not seem a good explanation. Another possibility is that regions differ in the scale of their functional organisation: the larger this scale, the more benefit we can expect from higher levels of smoothing.

4.2. Spatial organisation

Finally, when comparing different conditions, we found the same pattern for all levels of smoothing in the motor, prefrontal, and low-level auditory cortex. Namely, we can distinguish between neural activity patterns coming from different hands, but not from the same hand. Even without smoothing, we found no significant difference between the same-finger and same-hand conditions. This seems to contradict the idea of hyperacuity, i.e., that it is possible to pick up functional organisation smaller than a voxel size using MVPA. Note that in the current study we might simply lack the ability to pick up signals of the supposedly smallest spatial scale. Importantly, the pattern was somewhat different in the high-level auditory cortex. In this region only, we can distinguish between neural activities from same-finger and same-hand conditions for the lowest smoothing levels (0 and/or 2,5mm FWHM), mostly for the second approach. Of course, the selectivity in the auditory cortex reflects the auditory cues that are quite different in these conditions.

4.3. Effect of analysis approach

We used two approaches to analyse the data. For the first approach, we followed the fMRI data analysis pipeline that is often used, in which smoothing is part of the pre-processing. Although frequently used, there is a major drawback of this type of smoothing: noise from voxels outside a ROI - which can even be in white matter - can contaminate the signal inside the ROI (Alink et al., 2013). This effect gets stronger with higher extents of smoothing. Nevertheless, including this approach was important, as future studies will likely use this

smoothing approach. In the second approach, we omit the data from voxels outside the ROI and only smooth the signal with voxels inside the ROI. When comparing these two approaches, we did not notice major differences, as the large trends remained the same. Nevertheless, there were some small changes in the results (e.g., results that are not significant for the second approach that were for the first one when looking at the effect of smoothing), and more pronounced changes in individual patterns for each participant.

Another possible way to approach the analysis of these data would be to use spatial band pass filtering, which has been shown to affect MVPA results as well (Alink et al., 2013; Sengupta et al., 2017). A full exploration of all possible filtering approaches is beyond the scope of the current study in which we focus upon the most commonly used approach of spatial smoothing. Nevertheless, bandpass filtering is a very fruitful approach to obtain additional insight as to why MVPA results are influenced by filtering of the data.

4.4. Recommendation for researchers

The question remains: how can researchers choose the optimal level of smoothing based on careful examination? Although it might seem helpful to state a general rule on the best smoothing level to use, this is a difficult - if not impossible - recommendation to make. Different studies use different techniques and approaches, and the effect of smoothing is not necessarily the same for different brain regions. For example, when looking at the motor cortex, smoothing with a 5, 7.5 or 10 mm kernel would probably be best, as both the difference between diagonal and non-diagonal ánd the difference between the same- versus different-hand conditions is optimised. Which one exactly should not matter, since small differences should not affect the results when findings are strong and consistent. For the other brain regions in this article, we might have chosen different optimal levels of smoothing, as they show a different trend.

In general, our results show that smoothing is generally advantageous, which is the most important message for readers to remember. Nonetheless, examining the effect of smoothing is vital when researchers suspect it will influence their results. As an interesting example, Gardumi and colleagues (2016) studied the effect of smoothing on their dataset and decided to use the optimal smoothing level only after careful examination.

References

Adrian, E. D., & Matthews, B. H. C. (1934). The berger rhythm: Potential changes from the occipital lobes in man. *Brain*. https://doi.org/10.1093/brain/57.4.355

Alink, A., Krugliak, A., Walther, A., & Kriegeskorte, N. (2013). fMRI orientation decoding in V1 does not require global maps or globally coherent orientation stimuli. *Frontiers in Psychology*, *4*(AUG), 1–14. https://doi.org/10.3389/fpsyg.2013.00493

Biasiucci, A., Franceschiello, B., & Murray, M. M. (2019). Electroencephalography. In *Current Biology*. https://doi.org/10.1016/j.cub.2018.11.052

Brants, M., Baeck, A., Wagemans, J., & Op de Beeck, H. P. (2011). Multiple scales of organization for object selectivity in ventral visual cortex. *NeuroImage*, *56*(3), 1372–1381. https://doi.org/10.1016/j.neuroimage.2011.02.079

Bullock, M., Jackson, G. D., & Abbott, D. F. (2021). Artifact Reduction in Simultaneous EEG-fMRI: A Systematic Review of Methods and Contemporary Usage. *Frontiers in Neurology*, *12*, 193.

Buxton, R. B. (2009). Introduction to functional magnetic resonance imaging: Principles and techniques. In *Introduction to Functional Magnetic Resonance Imaging: Principles and Techniques*. https://doi.org/10.1017/CBO9780511605505

Carlson, T. (2014). Orientation Decoding in Human Visual Cortex: New Insights from an Unbiased Perspective. *Journal of Neuroscience*, *34*(24), 8373–8383. https://doi.org/10.1523/JNEUROSCI.0548-14.2014

Chaimow, D., Yacoub, E., Ugurbil, K., & Shmuel, A. (2011). Modeling and analysis of mechanisms underlying fMRI-based decoding of information conveyed in cortical columns. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2010.09.037

Clifford, A., Franklin, A., Holmes, A., & Davies, I. R. L. (2011). Investigating the underlying mechanisms of categorical perception of colour using the Event-Related Potential technique. In *New Directions in Colour Studies* (Issue 0, pp. 1–24). https://doi.org/10.1075/z.167.28cli

Clifford, C. W. G., & Mannion, D. J. (2015). Orientation decoding: Sense in spirals? *NeuroImage*, *110*, 219–222. https://doi.org/10.1016/j.neuroimage.2014.12.055

Cohen, M. X. (2017). Where Does EEG Come From and What Does It Mean? In *Trends in Neurosciences*. https://doi.org/10.1016/j.tins.2017.02.004

Downing, P. E., Wiggett, A. J., & Peelen, M. V. (2007). Functional magnetic resonance imaging investigation of overlapping lateral occipitotemporal activation using multi-voxel pattern analysis. *J Neurosci*, *27*(1), 226–233. https://doi.org/10.1523/JNEUROSCI.3619-06.2007

Feinberg, D. A., & Yacoub, E. (2012). The rapid development of high speed, resolution and precision in fMRI. *Neuroimage*, *62*(2), 720–725.

Fox, P. T., & Raichle, M. E. (1986). Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.83.4.1140

Freeman, J., Brouwer, G. J., Heeger, D. J., & Merriam, E. P. (2011). Orientation decoding depends on maps, not columns. *J Neurosci*, *31*(13), 4792–4804. https://doi.org/10.1523/JNEUROSCI.5160-10.2011

Freeman, J., Heeger, D. J., & Merriam, E. P. (2013). Coarse-Scale Biases for Spirals and Orientation in Human Visual Cortex. *Journal of Neuroscience*, *33*(50), 19695–19703. https://doi.org/10.1523/JNEUROSCI.0889-13.2013

Friston, K. J. (2003). Experimental Design and Statistical Parametric Mapping. In *Human Brain Function: Second Edition*. https://doi.org/10.1016/B978-012264841-0/50033-0

Friston, K. J. (2011). Functional and Effective Connectivity: A Review. *Brain Connectivity*.

https://doi.org/10.1089/brain.2011.0008

Friston, K. J., Josephs, O., Rees, G., & Turner, R. (1998). Nonlinear event-related responses in fMRI. *Magnetic Resonance in Medicine*, *39*(1), 41–52.

Gardumi, A., Ivanov, D., Hausfeld, L., Valente, G., Formisano, E., & Uludağ, K. (2016). The effect of spatial resolution on decoding accuracy in fMRI multivariate pattern analysis. *NeuroImage*, *132*, 32–42. https://doi.org/10.1016/j.neuroimage.2016.02.033

Gillebert, C. R., & Mantini, D. (2013). Functional connectivity in the normal and injured brain. In *Neuroscientist*. https://doi.org/10.1177/1073858412463168

Goldman, R. I., Stern, J. M., Engel Jr, J., & Cohen, M. S. (2000). Acquiring simultaneous EEG and functional MRI. *Clinical Neurophysiology*, *111*(11), 1974–1980.

Greene, D. J., Black, K. J., & Schlaggar, B. L. (2016). Considerations for MRI study design and implementation in pediatric and clinical populations. *Developmental Cognitive Neuroscience*, *18*, 101–112.

Grill-Spector, K., Henson, R., & Martin, A. (2006). Repetition and the brain: Neural models of stimulus-specific effects. *Trends in Cognitive Sciences*, *10*(1), 14–23. https://doi.org/10.1016/j.tics.2005.11.006

Grill-Spector, K., & Malach, R. (2001). fMR-adaptation: A tool for studying the functional properties of human cortical neurons. *Acta Psychologica*. https://doi.org/10.1016/S0001-6918(01)00019-1

Haxby, J. V, Gobbini, M. I., Furey, M. L., Ishai, A., Schouten, J. L., & Pietrini, P. (2001). Distributed and overlapping representations of faces and objects in ventral temporal cortex. *Science*, *293*(September), 2425–2430. https://doi.org/10.1126/science.1063736

Haynes, J. D., & Rees, G. (2006). Decoding mental states from brain activity in humans. In *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn1931

Hendrick, R. E., Nelson, T. R., & Hendee, W. R. (1984). Optimizing tissue contrast in magnetic resonance imaging. *Magnetic Resonance Imaging*. https://doi.org/10.1016/0730-725X(84)90005-5

Horovitz, S. G., Rossion, B., Skudlarski, P., & Gore, J. C. (2004). Parametric design and correlational analyses help integrating fMRI and electrophysiological data during face processing. *Neuroimage*, *22*(4), 1587–1595.

Iidaka, T., Matsumoto, A., Haneda, K., Okada, T., & Sadato, N. (2006). Hemodynamic and electrophysiological relationship involved in human face processing: Evidence from a combined fMRI–ERP study. *Brain and Cognition*, *60*(2), 176–186.

İnce, R., Adanır, S. S., & Sevmez, F. (2020). The inventor of electroencephalography (EEG): Hans Berger (1873–1941). In *Child's Nervous System*. https://doi.org/10.1007/s00381-020-04564-z

Kamitani, Y., & Tong, F. (2005). Decoding the visual and subjective contents of the human brain. *Nature Neuroscience*, *8*(5), 679–685. https://doi.org/10.1038/nn1444

Kim, S., Richter, W., & Uğurbil, K. (1997). Limitations of temporal resolution in functional MRI. *Magnetic Resonance in Medicine*, *37*(4), 631–636.

Koster-Hale, J., Saxe, R., Dungan, J., & Young, L. L. (2013). Decoding moral judgments from neural representations of intentions. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.1207992110

Kriegeskorte, N., & Bandettini, P. (2007). Analyzing for information, not activation, to exploit high-resolution fMRI. In *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2007.02.022

Kriegeskorte, N., Cusack, R., & Bandettini, P. (2010). How does an fMRI voxel sample the neuronal activity pattern: Compact-kernel or complex spatiotemporal filter? In *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2009.09.059

Kriegeskorte, N., Mur, M., & Bandettini, P. (2008). Representational similarity analysis - connecting the branches of systems neuroscience. *Frontiers in Systems Neuroscience*, *2*(November), 4. https://doi.org/10.3389/neuro.06.004.2008

Lachaux, J. P., Rudrauf, D., & Kahane, P. (2003). Intracranial EEG and human brain mapping. *Journal of Physiology-Paris*, *97*(4–6), 613–628.

Lindquist, M. A., & Wager, T. D. (2016). Principles of functional Magnetic Resonance Imaging. In *Handbook of Neuroimaging Data Analysis* (pp. 139–174).

Logothetis, N. K. (2008). What we can do and what we cannot do with fMRI. In *Nature*. https://doi.org/10.1038/nature06976

Mannion, D. J., McDonald, J. S., & Clifford, C. W. G. (2009). Discrimination of the local orientation structure of spiral Glass patterns early in human visual cortex. *NeuroImage*, *46*(2), 511–515. https://doi.org/10.1016/j.neuroimage.2009.01.052

Miletić, S., Bazin, P.-L., Weiskopf, N., van der Zwaag, W., Forstmann, B. U., & Trampel, R. (2020). fMRI protocol optimization for simultaneously studying small subcortical and cortical areas at 7 T. *NeuroImage*, *219*, 116992.

Misaki, M., Luh, W. M., & Bandettini, P. A. (2013). The effect of spatial smoothing on fMRI decoding of columnar-level organization with linear support vector machine. *Journal of Neuroscience Methods*. https://doi.org/10.1016/j.jneumeth.2012.11.004

Möllenhoff, K., Oros-Peusquens, A. M., & Shah, N. J. (2012). Introduction to the basics of magnetic resonance imaging. *Neuromethods*. https://doi.org/10.1007/7657-2012-56

Mullinger, K., & Bowtell, R. (2011). Combining EEG and fMRI. In *Magnetic Resonance Neuroimaging* (pp. 303–326). Springer.

Norcia, A. M., Gregory Appelbaum, L., Ales, J. M., Cottereau, B. R., & Rossion, B. (2015). The steady-state visual evoked potential in vision research: A review. *Journal of Vision*. https://doi.org/10.1167/15.6.4

Norman, K. A., Polyn, S. M., Detre, G. J., & Haxby, J. V. (2006). Beyond mind-reading: multi-voxel pattern analysis of fMRI data. In *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2006.07.005

Nunez, P. L., & Srinivasan, R. (2006a). A theoretical basis for standing and traveling brain waves measured with human EEG with implications for an integrated consciousness. *Clinical Neurophysiology*. https://doi.org/10.1016/j.clinph.2006.06.754

Nunez, P. L., & Srinivasan, R. (2006b). *Electric fields of the brain: the neurophysics of EEG*. Oxford University Press, USA.

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.87.24.9868

Op de Beeck, H. P., Baker, C. I., DiCarlo, J. J., & Kanwisher, N. G. (2006). Discrimination training alters object representations in human extrastriate cortex. *Journal of Neuroscience*, *26*(50), 13025–13036. https://doi.org/10.1523/JNEUROSCI.2481-06.2006

Op de Beeck, Hans P. (2010). Against hyperacuity in brain reading: Spatial smoothing does not hurt multivariate fMRI analyses? *NeuroImage*, *49*(3), 1943–1948. https://doi.org/10.1016/j.neuroimage.2009.02.047

Op de Beeck, Hans P, Haushofer, J., & Kanwisher, N. G. (2008). Interpreting fMRI data: maps, modules and dimensions. *Nature Reviews. Neuroscience*, *9*(2), 123–135. https://doi.org/10.1038/nrn2314

Parkes, L. M., Schwarzbach, J. V, Bouts, A. A., Deckers, R. R., Pullens, P., Kerskens, C. M., & Norris, D. G. (2005). Quantifying the Spatial Resolution of the Gradient Echo and Spin Echo BOLD Response at 3 Tesla. *Magnetic Resonance in Medicine*, *54*, 1465–1472. https://doi.org/10.1002/mrm.20712

Pauling, L., & Coryell, C. D. (1936). The Magnetic Properties and Structure of Hemoglobin, Oxyhemoglobin and Carbonmonoxyhemoglobin. *Proceedings of the National Academy of Sciences*. https://doi.org/10.1073/pnas.22.4.210

Poldrack, R. A., Nichols, T., & Mumford, J. (2011). Handbook of Functional MRI Data Analysis. In *Handbook of Functional MRI Data Analysis*. https://doi.org/10.1017/cbo9780511895029

Ritter, P., & Villringer, A. (2006). simultaneous EEG–fMRI. *Neuroscience & Biobehavioral Reviews*, *30*(6), 823–838.

Sadeh, B., Podlipsky, I., Zhdanov, A., & Yovel, G. (2010). Event-related potential and functional MRI measures of face-selectivity are highly correlated: A simultaneous ERP-fMRI investigation. *Human Brain Mapping*. https://doi.org/10.1002/hbm.20952

Sah, P., Faber, E. S. L., Lopez de Armentia, M., & Power, J. (2003). The amygdaloid complex: anatomy and physiology. *Physiological Reviews*, *83*(3), 803–834.

Sengupta, A., Yakupov, R., Speck, O., Pollmann, S., & Hanke, M. (2017). The effect of acquisition resolution on orientation decoding from V1 BOLD fMRI at 7 Tesla. *NeuroImage*, *148*(January), 64–76. https://doi.org/10.1016/j.neuroimage.2016.12.040

Swisher, J. D., Gatenby, J. C., Gore, J. C., Wolfe, B. A., Moon, C. H., Kim, S. G., & Tong, F. (2010). Multiscale pattern analysis of orientation-selective activity in the primary visual cortex. *J Neurosci*, *30*(1), 325–330. https://doi.org/30/1/325 [pii]\r10.1523/JNEUROSCI.4811-09.2010

Swisher, J., & Tong, F. (2012). More than maps: the fMRI orientation signal persists after removal of radial bias. *Journal of Vision*, *12*(9), 1124–1124. https://doi.org/10.1167/12.9.1124

Teplan, M. (2002). Fundamentals of EEG measurement. *Measurement Science Review*, *2*(2), 1–11.

Thulborn, K. R., Waterton, J. C., Matthews, P. M., & Radda, G. K. (1982). Oxygenation dependence of the transverse relaxation time of water protons in whole blood at high field. *BBA - General Subjects*. https://doi.org/10.1016/0304-4165(82)90333-6

Tudor, M., Tudor, L., & Tudor, K. I. (2005). [Hans Berger (1873-1941)--the history of electroencephalography]. *Acta Medica Croatica : Casopis Hravatske Akademije Medicinskih Znanosti*.

Yoo, P. E., John, S. E., Farquharson, S., Cleary, J. O., Wong, Y. T., Ng, A., Mulcahy, C. B., Grayden, D. B., Ordidge, R. J., & Opie, N. L. (2018). 7T-fMRI: Faster temporal resolution yields optimal BOLD sensitivity for functional network imaging specifically at high spatial resolution. *Neuroimage*, *164*, 214–229.

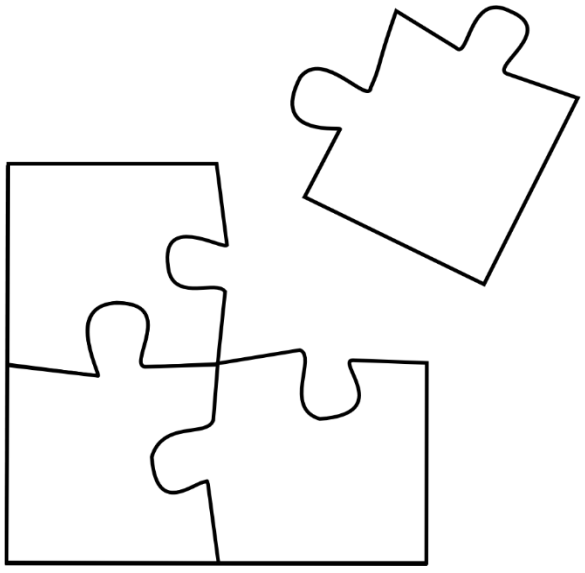
Yoo, S., Talos, I., Golby, A. J., Black, P. M., & Panych, L. P. (2004). Evaluating requirements for spatial resolution of fMRI for neurosurgical planning. *Human Brain Mapping*, *21*(1), 34–43.

Yovel, G. (2016). Neural and cognitive face-selective markers: an integrative review. *Neuropsychologia*, *83*, 5–13.

PART II

Face processing

in autism spectrum disorder



Overview Part II

In this second part of my dissertation, I discuss the complex and extraordinary human skill of face processing. Face processing has been studied extensively over the last decades, in groups of all ages, with and without (psychiatric) conditions, and using different experimental techniques. The neural underpinnings of face processing have often been investigated, using a myriad of different designs and neuro-imaging techniques, among which the techniques described above. Considering that difficulties in face processing are suggested to be at the root of social difficulties in individuals with ASD, I used the techniques described in Part I to study face processing in (young) adults with and without autism spectrum disorder (ASD).

I start this section by providing the reader with a detailed background into the main topics of study: the processing of faces and autism spectrum disorder. Next, I present two empirical studies in which I investigated the neural underpinnings of face processing. In the first study, fMRI was used to acquire neuro-imaging data, as outlined in the first section of Chapter 1. In line with our findings in Chapter 2, showing that moderate amounts of smoothing have an advantageous effect on the results of MVPA, a kernel of two times the voxel size was used to smooth the data. In the second study, EEG was the neuro-imaging method of choice, and data was treated as described in the second section of Chapter 1. Finally, I will wrap up my dissertation with a discussion of the results, placing them in the broad context of face processing as well as ASD research and providing possible future directions, to end with a general conclusion.

Chapter 3

Introduction to face processing and autism spectrum disorder

Summary Chapter 3

As humans, we are highly social creatures. Faces play a crucial role in social communication and provide a wealth of information. To communicate well, we must be able to process both the identity of a person ('Who is it?') and their facial expressions ('What is this person feeling?') with a high level of accuracy and speed. Luckily, most of us can rely on our expert levels of face processing (Tanaka, 2001; Tanaka & Gauthier, 1997). Nonetheless, individuals with autism spectrum disorder can experience difficulties in both facial identity and facial expression processing (Barton et al., 2004). In this dissertation, the main object of study has been the neural basis of face processing in adults with autism spectrum disorder and their neurotypical counterparts.

In this chapter, the reader is introduced to important literature and concepts. In the first section, I provide an overview of relevant literature regarding face processing, both at a behavioural and at a neural level. Secondly, a characterisation of autism spectrum disorder (ASD) is outlined. Next, I describe face processing research in the ASD population, focusing on the differences between individuals with and without ASD. Finally, I discuss potential mechanisms that might play a role in ASD-related atypicalities in face processing.

1. Face processing

Our eyes are undoubtedly indispensable to discover the world around us. However, we need our brain to make sense of what our eyes are seeing. First, neural signals are sent to the occipital cortex, where the processing of visual information starts in the primary visual cortex (V1). From V1, the neural signals gradually progress to higher-level brain regions into two separate visual streams: the dorsal 'where/how' pathway, and the ventral 'what' pathway (Ungerleider & Mishkin, 1982). The 'where/how' pathway ends in the posterior parietal cortex. Its function is to visually guide action by encoding the location of an object, and subsequently guiding the 'reach and grab' of the object. On the other hand, the 'what' pathway ends in the inferior temporal cortex (IT). Its function is to recognise and identify objects in the world around us. Recently, the existence of a third visual pathway has been suggested (Pitcher & Ungerleider, 2021), located somewhat in between, ending in the superior temporal sulcus. This third pathway is thought to specialise in social perception.

Faces are 'special' objects. Humans have an innate preference for faces over other objects from the moment they are born (Johnson et al., 1991, 2015). Authors indeed argue that new-borns have a pre-wired attentional bias towards faces, although the mechanisms behind this face preference are still debated (Simion & Giorgio, 2015). Additionally, face processing seems to rely on different mechanisms than the processing of other objects, as findings indicate that face perception can be selectively impaired in brain-damaged patients, and prosopagnosia can exist without the presence of object agnosia (Busigny et al., 2010; Duchaine & Nakayama, 2006; Moscovitch et al., 1997; Riddoch et al., 2008). In the healthy brain, face specificity was identified based on the finding that inversing faces decreased performance to a larger extent than the inversion of other objects (Yin, 1969). Later, it was discovered that the reason for this face inversion effect was a more holistic perception of faces (Tanaka & Farah, 1993; Tanaka & Simonyi, 2016). Since, there has been an abundance of research on face processing.

1.1. Face-responsive brain regions

A myriad of brain regions is thought to be directly or indirectly involved in face processing. Here, I discuss several brain areas that are indispensable for face processing, and/or respond more strongly to faces in general or certain aspects of a face, compared to other stimuli.

A first brain region is the *inferior occipital cortex*, which houses the "Occipital Face area" (OFA), a region argued to be necessary for accurate face perception (Pitcher, Walsh, et al., 2011; Rossion, Caldara, et al., 2003). Studies show the OFA preferentially represents parts of faces, for instance mouth or eyes (Fox, Moon, et al., 2009; Rotshtein et al., 2005). This is in line with the hypothesis that the inferior occipital region represents low-level facial features and carries out early face perception (Haxby, Hoffman, et al., 2000). The OFA is primarily sensitive to changes in form information of faces and seems to play a role in both facial identity and expression processing (Pitcher et al., 2008, 2009; Pitcher, Walsh, et al., 2011; Rotshtein et al., 2005). Finally, it responds more strongly to dynamic stimuli (Furl et al., 2015; Pitcher, Dilks, et al., 2011).

Secondly, the *fusiform cortex* is situated within the inferior temporal cortex, and it houses the "Fusiform Face Area" (FFA) (Kanwisher et al., 1997). Here, the 'most consistent and robust face-selective activation' is found (pp. 2112, Kanwisher & Yovel, 2006). Indeed, the FFA responds more strongly to faces than houses or hands, and more strongly to intact faces than scrambled faces, indicating the region is indeed selective to faces. In contrast to the OFA, the FFA is not primarily sensitive to lower-level facial features (Kanwisher & Yovel, 2006; Pitcher, Walsh, et al., 2011). Research suggests that the FFA is mainly sensitive to changes in identity, indicated by significant decoding of identity (Axelrod & Yovel, 2015; Goesaert & Op de Beeck, 2013; Nestor et al., 2011) and adaptation to same identity faces (Grill-spector et al., 2004; Rotshtein et al., 2005; Winston et al., 2004). In addition, the fusiform gyrus shows higher activation to emotional than neutral faces (Fusar-poli et al., 2009; Sabatinelli et al., 2011), and adaptation to emotional faces (Cohen Kadosh et al., 2010; Fox, Moon, et al., 2009; Xu & Biederman, 2010). Finally, the FFA does not appear to be particularly sensitive to motion, as its response to dynamic stimuli is not always higher than the response to static stimuli (Furl et al., 2013, 2015; Lee et al., 2010; Pitcher et al., 2014; Pitcher, Dilks, et al., 2011). Only dynamic stimuli showing morphed facial expressions seem to consistently activate the FFA more than static faces (Arsalidou et al., 2011; LaBar et al., 2003; Pelphrey et al., 2007; Sato et al., 2004).

Thirdly, the *superior temporal* region, including the superior temporal sulcus (STS), is thought to be involved in the variant aspect of faces (Hoffman & Haxby, 2000; Ishai et al., 2005; Puce et al., 1998; Wicker et al., 1998). Research shows that the STS is more sensitive to dynamic than static faces, regardless of whether these faces are neutral or expressive (Furl et al., 2013, 2015; Lee et al., 2010; Pitcher, Dilks, et al., 2011). Rather than to 'random' motion, it responds to biological movement (Grossman et al., 2000; Grossman et al., 2005) and especially facial movements (Pitcher et al., 2014; Puce et al., 1998). Moreover, the STS responds particularly strong to meaningful rather than random facial movements, confirming its role in the processing of socially meaningful facial movement (Campbell et al., 2001). While the STS seems to play a role in processing dynamic facial identity as indicated by significant decoding of facial identities (Dobs et al., 2018), its role in identity processing of static faces is limited, demonstrated by a lack of adaptation to same identity faces (Mazard et al., 2006; Yovel & Kanwisher, 2005) and a lack of significant decoding of facial identities (Axelrod & Yovel, 2015; Wegrzyn et al., 2015; Zhang et al., 2016).

Fourthly, the *amygdala* can be found subcortically and is mainly involved in the perception of emotional expressions (Adolphs, 2008), demonstrated by a release of adaptation to changes in expression but not identity of dynamic faces (Harris et al., 2014). Moreover, research using implanted electrodes has shown that the amygdala encodes subjective judgements of expressive faces rather than more objective form information (Wang et al., 2014). Furthermore, it seems to retrieve most information from the eye region of faces, as lesions of the amygdala lead to an inability to spontaneously fixate the eye region, causing impairments to recognise facial expressions (Adolphs et al., 2005). In addition, it has been suggested that the amygdala responds more strongly to salient faces (i.e., faces requiring a response), without them necessarily having to be expressive (Guex et al., 2020; Santos et al., 2011).

Fifthly, the *inferior frontal gyrus* is thought to be involved in semantic knowledge about faces (Brambati et al., 2010; Ishai, 2008). Accordingly, stronger activation is observed in this region when viewing familiar faces compared to newly learned faces (Leveroni et al., 2000). In addition, this region responds to the face of one's partner more than one's own face (Taylor et al., 2009). This implies familiarity itself is not driving the activation, but rather the monitoring of information, which is in line with strong connections between inferior frontal and temporal regions (such as the anterior temporal cortex discussed below).

Finally, the *anterior temporal cortex* (anterior temporal lobe, ATL) is thought to be involved in processing the individual identity of a face, as indicated by adaptation to familiar faces

(Nakamura et al., 2000; Sugiura et al., 2001) and the ability to discriminate facial identities using multi-voxel pattern analyses (Kriegeskorte et al., 2007; Nestor et al., 2011). Furthermore, the anterior temporal cortex shows higher selectivity (Rotshtein et al., 2005) and greater adaptation (Sugiura et al., 2011) to familiar than to non-familiar faces. As such, ATL is thought to be involved in the highest levels of face processing (Jonas et al., 2016). It is likely involved in retrieving semantic knowledge about a perceived identity, as lesion studies show a selective impairment to identification of faces, and not differentiation between individuals (e.g., Tranel et al., 1997).

1.2. Face processing frameworks and considerations

1.2.1. The model of Bruce & Young

In 1986, a cognitive model to describe face processing was proposed (Bruce & Young, 1986). This model was based on evidence from cognitive as well as neuropsychological studies and incorporated various aspects of face processing, including face identity, expression, and semantic information. In the model, face processing starts from a single point of view, similar to a static picture of a face. From this viewer-centred representation, a more abstract facial representation is formed that allows for recognition across different head angles, illumination levels, and expressions. To recognise facial identity, the abstract facial representation must be matched with a stored facial representation, which in turn activates semantic information about this person. In contrast, expression is believed to be processed disregarding familiarity, based solely on a viewer-centred representation (i.e., no abstraction). More specifically, facial emotions are coded based on the configuration of different facial features. This model does not include a neuroanatomical basis of face processing, as only non-primate studies and lesion studies were available at the time (Young & Bruce, 2011).

1.2.2. The model of Haxby and colleagues

In 2000, an influential neural face processing model was suggested by Haxby and colleagues (Haxby, Hoffman, et al., 2000). In this model, a distinction is made between the processing of variant and invariant facial features. The processing of invariant facial features plays a key role in identity recognition, while variant aspects of the face aid social communication such as expression recognition (Hoffman & Haxby, 2000).

Neuro-anatomically, the processing of invariant facial features is associated with stronger activity in inferior temporal (e.g., the fusiform face area, FFA) and inferior occipital regions (e.g., the occipital face area, OFA) (Kanwisher & Yovel, 2006). On the other hand, variant aspects of faces are thought to be processed by the superior temporal cortex (e.g., the superior temporal sulcus, STS) (Puce et al., 1998; Wicker et al., 1998). This three-region core network processes the visual information and is complemented by an extended brain network supporting the further processing and interpretation of facial information (Haxby et al., 2002). As part of this extended face processing network, the anterior temporal cortex has been implicated for biographical knowledge assisting identity processing (Gorno-Tempini et al., 1998; Leveroni et al., 2000). Furthermore, the amygdala and the inferior frontal cortex are thought to play a crucial role in the processing of emotion (Adolphs & Tranel, 1999; Brothers, 1990; Haxby, Petit, et al., 2000; Sprengelmeyer et al., 1998).

1.2.3. Considerations: possible alterations and extensions

In recent years, the models described above have been subject to proposed alterations and extensions. Here, some suggestions are outlined, most of which are presented in publications by Bernstein and Yovel (2015) and Duchaine and Yovel (2015).

1.2.3.1. Heightened activation to dynamic faces

O'Toole and colleagues (2002) proposed modifications to account for dynamic face processing. First, the role of the STS is extended to not only include processing of invariant features (e.g., expression), but also entail processing of dynamic identity information or so-called 'dynamic facial signatures'. These person-specific facial signatures can only contribute to identity recognition for familiar faces since we must know someone's idiosyncratic facial movements. Secondly, the authors suggest a one-way interaction between the dorsal and the ventral face processing stream. More specifically, they propose that dynamic information is processed in the dorsal stream and sent to the ventral stream as static form information.

Interestingly, a very recent revision of Ungerleider and Mishkin's (1982) dorsal 'where' and ventral 'what' pathways suggested the existence of a third visual pathway (Pitcher & Ungerleider, 2021). This third pathway starts in V1 and projects into the superior temporal sulcus. It is thought to specialise in social perception, among which the processing of

dynamic faces. Research indeed shows that responses to dynamic stimuli are heightened in the STS, but also other social brain regions like the inferior frontal gyrus (IFG) and the amygdala (Fox, Iaria, et al., 2009; Kilts et al., 2003; Pitcher, Dilks, et al., 2011). Even ventral regions are sometimes found to respond more strongly to dynamic stimuli (e.g., Schultz & Pilz, 2009), although a preference to dynamic stimuli in the FFA and the OFA is not always observed (Pitcher, Dilks, et al., 2011). Together, these findings suggest that dorsal face-responsive areas in particular, but also other face-responsive areas, are sensitive to motion in faces.

1.2.3.2. Multiple face processing pathways

Duchaine and Yovel (2015) suggest a separate set of pathways into the face processing network, based on lesion-studies and neuroimaging results. More specifically, ventral (OFA-FFA) and dorsal (STS) pathways are proposed to be separate (Duchaine & Yovel, 2015). Lesion studies have shown that impairments in the OFA and/or the FFA do not necessarily cause problems with face perception, and that face-responsive activation in other, undamaged regions can remain intact (Dalrymple et al., 2011; Sorger et al., 2007; Steeves et al., 2006). Research on the connectivity between face-responsive brain areas supports the suggestion of multiple pathways. Using diffusion tensor imaging, strong connections were shown between the OFA and the FFA, but not between either the OFA or the FFA and the STS (Gschwind et al., 2012; Pyles et al., 2013). Furthermore, these results are in line with findings of functional connectivity studies, reporting the OFA and the FFA to be more strongly connected than either of them to the STS (Avidan et al., 2014). Finally, findings of a combined transcranial magnetic stimulation (TMS)-fMRI study support the idea of multiple pathways (Pitcher, 2014). After TMS to the OFA, the response in the STS decreased in response to static faces but not dynamic faces, while after TMS to the STS itself, the response decreased in response to dynamic but not static faces. This indeed suggests a dissociation between the pathways involved in face processing, more specifically in terms of facial movement.

1.2.3.3. Timing of face processing

To investigate the timing of face-responsive neural activation, studies using simultaneous EEG-fMRI and TMS have been carried out. Results have indicated distinct timings for different face-responsive regions. Activation in the OFA was correlated with EEG face-

selectivity at 110 – 120 ms after stimulus onset, while activation in the FFA and the STS was correlated with EEG face-selectivity at 150 – 180 ms after stimulus onset, indicating face-selective activation in the OFA precedes face-selective activation in the FFA and the STS (Sadeh et al., 2010). Likewise, using TMS, Pitcher and colleagues (2012) were able to identify the time-window in which the OFA contributes to face processing, as pulses at 100 – 110 ms disrupted performance. The time-window in which the STS contributes to face processing seems to be 100-140 ms, indicating face processing in the STS starts around the same time as in the OFA, but lasts longer (Pitcher, 2014).

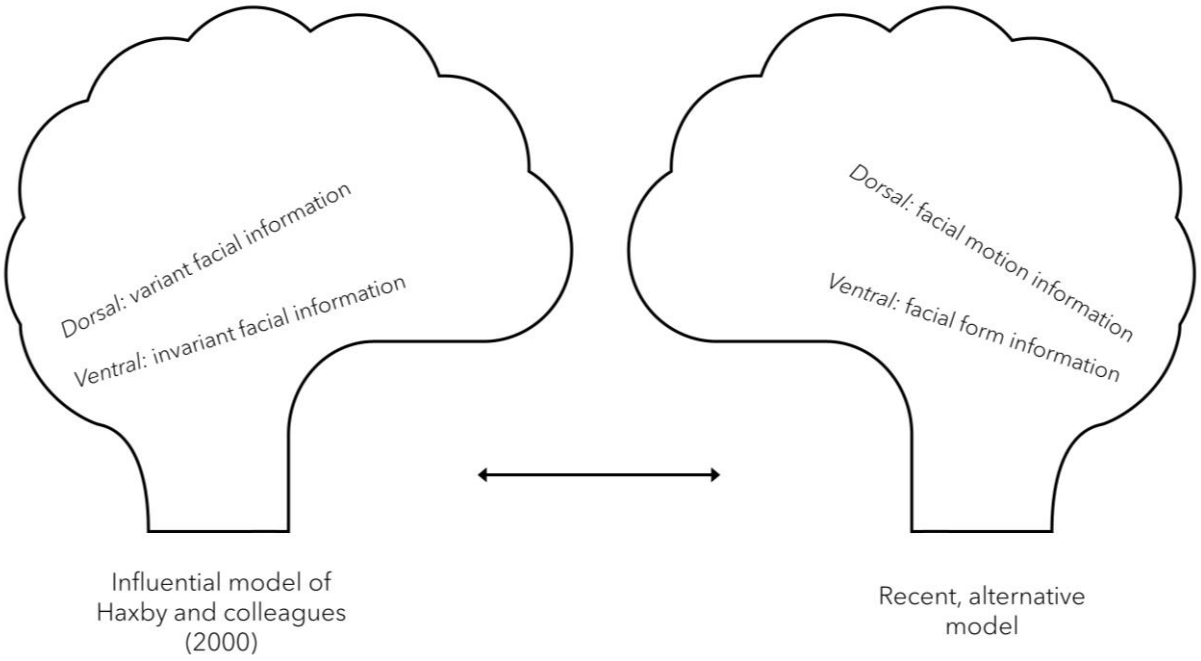


Figure 3.1. Comparison between the influential face processing models. Left model, proposed by Haxby et al. (2000), argues that invariant facial information - mostly involving facial identity - is processed in the ventral stream (inferior occipital and fusiform cortex), while variant information – including processing of facial expressions and other social cues – is processed by the dorsal stream (superior temporal sulcus). Right model is a recent, alternative face processing model proposed by Duchaine and Yovel (2015). The alternative model suggests that the ventral stream processes (static) form information of faces – including identity and expression-, while the dorsal stream processes motion information including dynamic identity features and facial expression movements.

1.2.3.4. Taking all modifications and extensions into consideration

In 2015, a new neural framework for face processing was proposed by Duchaine and Yovel (2015). Taking together new evidence and the suggested changes to earlier models, they suggest looking at the dorsal and ventral visual streams differently compared to the influential model proposed by Haxby and colleagues (2000) (Figure 3.1). In their proposed framework, the dorsal stream extracts motion information (of both identity and expression) instead of variant facial information. In addition, it may also process 'motion from form' information, for instance implied motion from a static expressive face. On the other hand, the ventral stream processes form information (of both identity and expression), instead of invariant facial features. The streams are considered to be separate, meaning the OFA is not the main entry point. This is in line with the recently proposed third visual pathway, projecting into the STS and involved in social perception including dynamic face processing (Pitcher & Ungerleider, 2021).

1.2.4. Identity and expression: dependent or independent processes?

Finally, we discuss the debate about facial identity and expression processing as separate or intertwined processes. In the dominant view proposed by Haxby and colleagues (2000), facial identity and expression are represented by two distinct but parallel neural routes. Arguments in favour of this two-pathway framework seem extensive: brain lesions selectively impair identity recognition and expression recognition, the familiarity of a face does not influence the ability to recognise expressions, and different populations of neurons respond to facial identity and facial expression in non-human primates (Calder & Young, 2005). In addition, Haxby and colleagues (2000) argue that when a change in expression occurs, it is not usually (mis)interpreted as a change in identity.

On the other hand, Calder & Young (2005) suggest that other frameworks might do a better job explaining the evidence at hand, arguing that evidence in favour of the two-pathway framework is not as strong as formerly believed. For instance, prosopagnosia patients do not usually have a fully intact expression recognition (Calder & Young, 2005). More recent work has indeed suggested a higher degree of overlap between identity and emotion processing. Accordingly, research suggests that regions involved in processing of identity are also activated when processing facial expressions, and vice versa. For example, the superior temporal sulcus also responds to identity (Dobs et al., 2018; Fox et al., 2011), and the fusiform gyrus is activated when processing expressions (LaBar et al., 2003; Pessoa

et al., 2002; Schultz & Pilz, 2009) and shows adaptation to emotional faces (Cohen Kadosh et al., 2010; Fox, Moon, et al., 2009; Xu & Biederman, 2010). The idea of multiple brain regions collaborating in a face processing network has been supported by other authors (e.g., Ishai, 2008; Tovée, 1998; Zhen et al., 2013). Finally, evidence supports a facilitation effect in which face processing is enhanced by integrating both identity and emotion of faces (Andrews & Ewbank, 2004; Winston et al., 2004; Yankouskaya et al., 2017). In sum, recent evidence suggests that - at least to some extent - facial identity and facial expression processes are related.

1.3. Face processing difficulties

Although most humans are considered to be experts in face processing, there are certain groups of individuals that can experience difficulties with the processing of faces, both regarding facial identity and facial expression.

1.3.1. Prosopagnosia

Prosopagnosia is described as the inability to recognise faces that cannot be explained by visual impairments or cognitive problems (e.g., amnesia). In other words, individuals with prosopagnosia fail to recognise who someone is (i.e., someone's identity) based on their facial features. The ability to recognise someone through other cues, such as voice, movement, or accessories, is intact (Mayer & Rossion, 2007). The condition can be congenital, usually with a strong family history, and its prevalence is estimated around 2,5% of the population (Kennerknecht et al., 2007, 2008). Less commonly, it is acquired later in life due to brain damage, such as stroke, traumatic brain injury or neurodegeneration. In addition, there are several types of prosopagnosia (De Renzi et al., 1991). Individuals that have the apperceptive variant of prosopagnosia fail to encode faces or facial features. Individuals with the second, associative variant can perceive the face but cannot recall the faces later.

The neural correlates of acquired prosopagnosia are widely varied, which is not surprising considering the complexity of the face processing network (Corrow et al., 2016). Interestingly, brain injuries can be linked to symptoms based on the division between occipitotemporal and anterior temporal damage (Barton, 2008). Individuals with occipitotemporal damage are more likely to have acquired the apperceptive variant of

prosopagnosia (Barton et al., 2002), while individuals with anterior temporal damage seem more likely to have acquired the associative variant (Kanwisher & Barton, 2011). In contrast, the neural correlates of congenital prosopagnosia remain subject of debate (Corrow et al., 2016).

1.3.2. Alexithymia

Alexithymia is a personality trait characterised by the difficulty to identify and describe emotions, including recognising facial expressions (Taylor, 1994). The aetiology of alexithymia is still debated, as various factors - such as traumatic experiences and even genetics - are thought to play a role (Jørgensen et al., 2007). With an estimated prevalence of 10% in the general population, it is fairly common (Franz et al., 2008). Alexithymia is considered a transdiagnostic deficit, meaning it is thought to be part of various disorders (Grynberg et al., 2012). At a neural level, alexithymia has been linked to hypoactivation of the amygdala when viewing emotional faces (Kugel et al., 2008; Meza-Concha et al., 2017; Reker et al., 2010).

1.3.3. Autism spectrum disorders

Autism spectrum disorder (ASD) is a neurodevelopmental disorder, characterised by difficulties in social communication. Individuals with ASD can experience difficulties with the recognition of both facial identities and facial expressions. More information will be provided in the next section.

The precise relation between ASD and prosopagnosia is still debated, although it has been suggested that prosopagnosia is more prevalent in the ASD population than in the general population (Cygan et al., 2018). Cases have been reported of individuals that have both prosopagnosia and ASD (Cygan et al., 2018; Kracke, 1994). Furthermore, one study found that individuals with ASD show more prosopagnosic traits, while individuals with prosopagnosia show more autistic traits compared to controls (Cook et al., 2015). How alexithymia and ASD relate to one another has recently been a subject of study. It has been argued that alexithymia can be a cause as well as a result of autistic traits (Poquérusse et al., 2018). Questions remain about the precise relationships between ASD and both prosopagnosia and alexithymia.

2. Autism spectrum disorder

2.1. History of autism

The origin of autism as a scientifically characterised disorder is an argument of debate. As early as the late 1930's, Dutch experts used the term 'autist' to describe children who 'lost feeling for or contact with reality', initially as a symptom of schizophrenia (Van Drenth, 2018). Only much later, this evolved into the description of an autonomous syndrome (Van Krevelen, 1952). During the Second World War, Leo Kanner and Hans Asperger published about the phenomenon of autism. Using terms as 'autistic psychopathy' (Asperger, 1944) and 'infantile autism' (Kanner, 1943), they described 'autism-like' behaviours in children, such as social deficits and stereotypical behaviours. Autism spectrum disorder (ASD) was first described as a separate diagnosis in the Third Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) in 1980 (American Psychiatric Association, 1980).

2.2. Characterisation of autism spectrum disorder

2.2.1. Diagnostic features

Today, we describe ASD as an early-onset neurodevelopmental disorder. In the DSM-5, it is characterised by deficits in two domains: social communication and interaction, and the presence of restricted and repetitive behaviours, interests, or activities (American Psychiatric Association, 2013). To diagnose ASD, these symptoms must be present from early childhood and impair daily functioning.

Difficulties with social communication and interaction are extensive and sustained. For a reliable diagnosis, information about social difficulties is based on multiple sources of information such as self-report, observations by parents, significant others, and the clinician. Often, individuals with ASD show language deficits, ranging from a complete lack of speech to difficulties with using speech in reciprocal social interactions. Difficulties in social interactions can range from a lack of reciprocity (e.g., one-sided requests) and reduced sharing of interests and emotions, to problems with responding to complex social cues, such as the moment and way to join an ongoing conversation. Non-verbally, individuals with ASD often exhibit atypical eye contact, facial expressions, and body

orientation. Individuals at the higher end of the spectrum have frequently developed compensatory strategies to cope, although they often still need to put in a lot of effort and can be anxious when confronted with complex social situations.

The second domain entails restricted and repetitive behaviours, interests, or activities. Restricted behaviours can include simple movements, such as hand flapping, and repetitive use of language, for example echolalia or the 'parroting' of heard words. Often, individuals with ASD display a certain kind of self-stimulation or 'stimming'. In addition, they are likely to adhere to patterns and routines, often referred to as 'insistence on sameness', and are actively resistant to change. Restricted interests in ASD are often overly intense, such as preoccupations with seemingly mundane objects. Special activities can be related to certain hypo- or hypersensitivities to sensory stimuli, such as fascinations to smells or lights. Individuals without language and intellectual disabilities are generally able to suppress repetitive behaviours. In this group, restricted interests and activities can be a source of possibility for education and employment.

2.2.2. Prevalence of ASD

Simply stating the prevalence of ASD is difficult, as rates vary widely across studied regions and even across time. One review - conducted on data from before 2012 - reported prevalence rates ranging from 0.01 to 1.89 % (Elsabbagh et al., 2012). A later review, focusing on prevalence estimates published since 2014, found prevalence rates between 0.08 and 9.3% (Chiarotti & Venerosi, 2020). The most plausible estimation of ASD prevalence is between 0.9 and 1.5 %, affecting four males for every female (Fombonne, 2020). These numbers have risen in recent decades, causing concern for a so-called 'epidemic of autism'. The increase in prevalence can be explained by changes in the autism characterisation and diagnostic criteria (Kim et al., 2014) as well as heightened awareness and improved detection (Fombonne, 2020).

Although the rise in numbers can be explained, there have been rumours about certain environmental factors causing autism. One example is the role of the measles, mumps, and rubella (MMR) vaccine in autism. This continues to be one of the most damaging controversies in vaccine safety, although there is strong evidence that the vaccine does not cause ASD (Destefano et al., 2019). There are two factors confirmed to increase the risk of autism: prenatal exposure to valproic acid (Christensen et al., 2013) and advanced paternal age (Hultman et al., 2011). Genetic factors, too, play an important role in autism, with meta-

analytic heritability estimates between 64 and 91% (Tick et al., 2016). This estimated range is very wide, reflecting the complex role of genetics in ASD, caused by both genetic and phenotypic heterogeneity (Persico & Napolioni, 2013).

2.3. Theoretical frameworks of autism spectrum disorder

Atypicalities in several cognitive processes are considered to be responsible for difficulties experienced by individuals with ASD (Happé, 2003), including perceptual style, social cognition, and executive functions. Accordingly, a myriad of theoretical frameworks has been proposed to account for ASD symptoms. These theories mostly focus on a specific symptom-cluster, such as perceptual or social symptoms. An overarching theory of ASD has been proposed with the predictive coding framework, which incorporates different clusters of symptoms.

2.3.1. Theories involving perception

It has been suggested that individuals with ASD show a local bias when processing stimuli, i.e., they more easily perceive the features of a stimulus instead of the stimulus as a whole. In this line of thinking, a popular framework is the *'weak central coherence'* account (Happé & Frith, 2006). It poses that individuals with ASD process stimuli more locally because they fail to extract the more global information. Rather than implying that it can explain social symptoms in ASD, the authors highlight that weak central coherence is but one aspect of ASD cognition existing alongside social cognition difficulties. A second theory with a focus on perceptual style is the *'enhanced perceptual functioning'* account of ASD (Mottron et al., 2006). The authors suggest that low-level processing is overdeveloped in individuals with ASD, resulting in a superior low-level perception and local perceptual style. Hence, they argue that there is indeed a preference for local information in ASD, but that a global perceptual style can be used when needed.

When considering complex social stimuli such as faces, these two theories yield different hypotheses. The global perception of faces is often studied using the face inversion effect. The weak central coherence account would predict that individuals with ASD have impaired global perception, and therefore an absent or diminished face inversion effect, while the enhanced perceptual functioning account would hypothesise a typical face inversion effect (Lahaie et al., 2006).

2.3.2. Theories involving social concepts

Social difficulties are among the key symptoms of ASD. One theory suggests that problems with theory of mind are at the root of social cognition difficulties (Baron-Cohen et al., 1985). The *theory of mind framework* poses that atypical (social) behaviour in ASD arises from difficulties in understanding the actions of others, as individuals with ASD fail to infer others' mental states such as emotions, beliefs, and intentions. A second social theory highlights the role of social motivation in ASD symptomatology. The *social motivation theory* (Chevallier et al., 2012) argues that less attentional weight is assigned to social information in ASD compared to neurotypicals, which causes decreased social orienting. An atypical (i.e., diminished) social reward system is likely at play, making social stimuli and interactions less rewarding for individuals with ASD (Clements et al., 2018). In turn, this decrease in social motivation can affect the development of typical social communication and cognition (e.g., theory of mind), and therefore account for ASD-related social difficulties.

Human faces are socially relevant stimuli. In that light, these theories can be applied to face processing. In the theory of mind framework, impairments in empathising with others could explain deficits in facial expression recognition (Baron-Cohen, 1991). On the other hand, the social motivation theory would predict general face processing difficulties in both identity and expression due to a lack of visual experience with faces (Oruc et al., 2018).

2.3.3. Predictive coding framework

The *predictive coding framework* of ASD (Van de Cruys et al., 2014) has aspired to provide an overarching theory to account for several clusters of ASD symptoms, among which the perceptual and social atypicalities described above. The predictive coding framework poses that the brain is constantly utilising current input and the current input's learned associations to generate predictions about future input, using a prediction model. The mismatch between the predicted input and the actual input is used to compute a prediction error. Based on this prediction error, the brain must decide. If the prediction error is considered informative, the prediction model needs to be updated to incorporate the newly learned information. If the prediction error is deemed uninformative, for example due to noise, it must be rejected and the prediction model stays in place. Here, the 'precision of the prediction error' comes into play, which is the weight assigned to the prediction error to indicate whether it is informative or not, i.e., used for new learning or ignored. All ASD symptoms are argued to be the consequence of an inflexibly high

precision of the prediction errors. In other words, individuals with ASD deem almost all prediction errors informative.

The social domain, among which the processing of faces, is thought to be most clearly affected by these inflexibly high precisions of the prediction error, as it is highly unpredictable and therefore requires a flexible precision of the prediction error. Faces are all highly similar stimuli, and we must rely on subtle differences to discriminate between faces or facial expressions. On the other hand, the same face can look very different due to 'noise': face orientation, lighting conditions, but also hairstyles and accessories. ASD-related difficulties in face perception are suggested to stem from a failure to flexibly assign high precision to informative prediction errors (i.e., based on small differences between diagnostic facial features such as bone structure or eye shape) and low precision to the uninformative prediction errors (i.e., based on viewpoint or changeable facial features). Instead, an inflexibly high precision of all prediction errors can cause the informative facial characteristics to be lost within the 'noise', causing difficulties with accurate perception of faces.

3. Face processing in ASD

Although most people can distinguish extraordinarily well between different facial identities and expressions (Tanaka, 2001; Tanaka & Gauthier, 1997), individuals with ASD can struggle with the processing of facial identity as well as facial expressions (Barton et al., 2004). These difficulties have been proposed to belong to the core deficits of ASD, underlying the ASD-related problems with social interaction (Dawson et al., 2005; Schultz, 2005; Tanaka & Sung, 2016).

Indeed, it becomes obvious from an early age that children with ASD have difficulties attending to and using facial information. In contrast to their neurotypical peers that display great interest in faces, children with ASD show poor eye contact and joint attention, as well as little attention to others, in line with the theory of mind framework (Baron-Cohen et al., 1985) and the social motivation theory of ASD (Chevallier et al., 2012). In addition, anecdotal evidence from individuals with ASD confirms that recognising people and knowing how they are feeling based on facial expressions can be challenging. For example, they testify that it can be difficult to recognise someone out of the familiar context, for instance when running into a colleague in the supermarket. Furthermore, changes in variable cues such as haircuts, glasses and clothing can cause difficulties when recognising faces that are not very familiar. Finally, individuals with ASD describe having problems with recognising facial emotions, particularly for complicated and ambiguous expressions. This can, of course, make adequate social interaction difficult.

In this section, I describe the empirical research regarding face processing in ASD, both at a behavioural and at a neural level. In addition, several mechanisms that may be at the root of face processing problems in ASD are discussed.

3.1. Behavioural studies about face processing in ASD

3.1.1. Facial identity processing

Research about *facial identity processing* in ASD has yielded mixed results. Reviews conclude that individuals with ASD generally – but not consistently - differ from neurotypical controls in terms of how well facial identities are discriminated. On simple perceptual tasks, in which faces are presented simultaneously, individuals with ASD do not perform worse

than their neurotypical counterparts. This finding holds across all investigated age groups (Weigelt et al., 2012). However, in one study, reaction times during a simple perceptual face processing task were found to be much higher in adults with ASD compared to neurotypical adults (Behrmann et al., 2006). Few other studies have included reaction times, of which most did not find differences between individuals with and without ASD across all age groups (Sterling et al., 2008). Slower reaction times were found in adults, but only during a first trial (Kleinhans et al., 2009), and in children, but only to unfamiliar faces (Pierce & Redcay, 2008). Further evidence suggests that individuals with ASD across all age groups perform worse on face processing tasks that include a (small) memory component, in which stimuli are not displayed simultaneously but sequentially, as well as on tasks with higher demands such as generalisation across poses or expressions (Weigelt et al., 2012). Taking together the evidence from studies using standardised tests such as the Benton Face Recognition Task (BFRT) and Cambridge Face Memory Task (CFMT), most research found face recognition in ASD to be impaired. Interestingly, all studies investigating adults with ASD observed impaired performances, while children with ASD and their neurotypical counterparts showed similar performance in some studies. One study investigated performance on the CFMT in different age groups, finding children and adolescents with ASD to be unimpaired while adults with ASD performed significantly worse compared to neurotypical adults (O'Hearn et al., 2010). These findings can be interpreted as evidence for a disruption of the typical developmental improvement in face recognition in ASD. In general, Weigelt and colleagues (2012) conclude that individuals with ASD have a specific difficulty for remembering faces, based on the finding that differences between groups are more likely to show up in studies that present facial stimuli successively (i.e., not simultaneously). Importantly, most studies investigating face recognition in individuals with ASD have found deficits to be specific to faces (Weigelt et al., 2012). This finding is in line with the social motivation theory of ASD (Chevallier et al., 2012), in which the lack of visual experience with faces is argued to result in difficulties with face processing.

It remains unclear whether different strategies for identity recognition are used by individuals with ASD (Tang et al., 2015; Weigelt et al., 2012). It has been suggested that individuals with ASD use different strategies (e.g., weak central coherence (Happé & Frith, 2006)), demonstrated by markers of atypical face processing such as a reduced face inversion effect (O'Brien et al., 2014; Tang et al., 2015; Vettori, Dzhelyova et al., 2019). However, these markers are often found to be typical in ASD across age groups (Hedley et al., 2015; Tavares et al., 2016; Weigelt et al., 2012). Altogether, there is no strong evidence

for qualitative differences in face recognition between individuals with and without ASD (Weigelt et al., 2012).

3.1.2. Facial expression processing

As in the case of facial identity processing, the empirical evidence regarding ASD-related difficulties in *facial expression processing* is mixed and inconsistent (Harms et al., 2010; Uljarevic & Hamilton, 2013). Some studies suggest a general deficit entailing all emotions (e.g., Luckhardt et al., 2017), which is supported by meta-analytic findings (Lozier et al., 2014). Other studies find specific difficulties, such as selective deficits in the recognition of negative emotions in individuals with ASD (e.g., Wallace et al., 2008; Wingenbach et al., 2017). Selective impairments in specific expressions are reported as well. It has been shown that fear (Lozier et al., 2014, Rump et al., 2009) and surprise (Law Smith et al., 2010) are difficult to recognise for individuals with ASD, especially adults. Happiness is often recognised equally well by individuals with and without ASD (Law Smith et al., 2010; Whitaker et al., 2017). Few studies find facial emotion recognition to be intact, and this finding has only been observed in children and adolescents (Lacroix et al., 2014; Leung et al., 2013; Tracy et al., 2011).

Task demands could play a role in the findings of impaired facial expression processing in individuals with ASD across age groups. The likelihood of observing deficits increases with higher task demands (Harms et al., 2010). For instance, group differences in emotion recognition have been observed when stimuli are only presented for a short time (Rump et al., 2009) or when stimuli are presented at low intensities (Griffiths et al., 2019; Wingenbach et al., 2017).

In general, studies observing intact expression recognition in ASD are rare, especially in adults. Research shows that the deficit in facial expression recognition is worse in adults than in children with ASD, as observed differences between individuals with ASD and their neurotypical counterparts grow more distinct with age (Lozier et al., 2014). The still ongoing development of facial emotion recognition in children possibly conceals differences between children with and without ASD. This implies that the skill does not improve similarly from childhood to adulthood in individuals with ASD compared to neurotypicals (Rump et al., 2009). These findings could be in line with the theory of mind framework of ASD (Baron-Cohen et al., 1985), as difficulties in recognising facial expressions can result from difficulties in empathising with others, as well as the social

motivation theory of ASD (Chevallier et al., 2012), which argues that difficulties in facial expression processing can result from lack of visual experience with faces due to lower social motivation.

3.1.3. Integration of facial identity and expression

Finally, evidence shows that face processing can be enhanced by *integrating facial identity and expression*, both in neurotypical controls and clinical populations (Yankouskaya et al., 2017). Interestingly, Oruc and colleagues (2018) found a correlation between the performance on an identity recognition task and an expression recognition task in individuals with ASD that was not present in neurotypicals. This suggests that the facial identity and facial expression recognition performances are similar in individuals with ASD, while neurotypicals might excel in the recognition of expressions but not identities or vice versa. This, in turn, might indicate a lack of social motivation as the origin of face processing difficulties in ASD (Chevallier et al., 2012), as both identity and expression are similarly affected.

3.2. Neuroimaging studies about face processing in ASD

3.2.1. Results of studies using fMRI

A myriad of studies has used fMRI as a tool to study face processing in individuals with and without ASD. Here, findings from different kinds of analyses are outlined.

Firstly, *neural activity* levels are often studied. Reviews show that inferior occipital, fusiform, superior temporal, and inferior frontal regions, as well as the amygdala have been found to be less active in individuals with ASD when looking at faces (Di Martino et al., 2009; Dichter, 2012; Nomi & Uddin, 2015; Philip et al., 2012). Studies specific to identity processing have shown the amygdala and fusiform, inferior frontal, superior temporal, and occipital cortices to be hypo-active in children, adolescents, and adults with ASD (Nomi & Uddin, 2015). In response to expressive faces, many studies have shown that the fusiform gyrus, the superior temporal sulcus, and the amygdala are less active in children, adolescents, and adults with ASD (Aoki et al., 2015; Di Martino et al., 2009; Dichter, 2012; Kleinhans et al., 2011; Nomi & Uddin, 2015; Philip et al., 2012). Occipital regions have also been found to be less reactive to expressive faces in children with ASD (Malisza et al., 2011). In contrast, the amygdala, the superior temporal sulcus, and occipital regions have been found to be more reactive to

expressive faces, but only in adults with ASD (Ashwin et al., 2007; Critchley et al., 2000; Hubl et al., 2003; Kleinhans et al., 2010). Interestingly, activation levels in some brain areas, among which the fusiform gyrus, are sensitive to training of facial expression processing (Bolte et al., 2006). In addition, oxytocin administration is associated with increased facial expression recognition in adolescents and adults with ASD, as well as increased activation in face-responsive brain regions (Domes et al., 2014). More specifically, oxytocin administration was found to increase the reactivity to facial stimuli in the amygdala, the superior temporal gyrus and the inferior frontal gyrus, among others.

Secondly, studies investigating *neural representations* that characterise facial identity and facial expression processing in ASD are sparse. It has been suggested that approaches focusing on neural patterns will better aid understanding of atypical face processing in ASD compared to univariate techniques because of a higher sensitivity (Nomi & Uddin, 2015). Accordingly, it has been suggested that fusiform activation patterns during face processing can reliably predict ASD symptom severity in children and young adults, with a better accuracy than (univariate) brain activations (Coutanche et al., 2011). Another study performed multi-voxel pattern analyses to study facial emotion processing using dynamic facial stimuli, finding no differences between adults with and without ASD (Kliemann et al., 2018). In terms of development, neural activation patterns typically grow more similar within a category (such as faces) with increasing age, but this evolution was not observed in ASD (O'Hearn et al., 2020). The authors found this development to be lacking in individuals with ASD in -among others- fusiform face area and inferior frontal gyrus, indicating that the typical specialisation of face processing from childhood to adulthood is possibly impaired in ASD.

Thirdly, *neural adaptation* has been used to study face processing in ASD. In general, it has been suggested that ASD symptoms – in particular hypo- and hypersensitivities to sensory input – might be associated with reduced sensory habituation in ASD (Jamal et al., 2021). Reduced behavioural habituation has indeed been observed in adults and children with ASD, both in the auditory and visual modality (Jamal et al., 2021; Lawson et al., 2015; Webb et al., 2010). At a neural level, evidence indicates reduced neural adaptation in both adults and children with ASD. Reduced habituation has been observed to neutral faces in the fusiform gyrus in adults (Ewbank et al., 2017) and the amygdala in children and adults with ASD (Kleinhans et al., 2009; Swartz et al., 2013). Furthermore, reduced neural adaptation to expressive faces was observed in the fusiform gyrus in adults (Kleinhans et al., 2016) as well as the amygdala in children and adults (Swartz et al., 2013; Tam et al., 2017). Research has

shown that reduced habituation in the amygdala and fusiform gyrus of adults with ASD is specific to face processing, as it is not reduced during the perception houses (Kleinhans et al., 2016).

Finally, *functional connectivity* between face-sensitive brain regions can be studied. In a neurotypical population, stronger connections between face-responsive brain areas - among which inferior occipital and superior temporal regions, as well as the fusiform gyrus and the amygdala - have been linked to better performance on face processing tasks (O'Neil et al., 2014; Zhang et al., 2009; Zhu et al., 2011). A generic underconnectivity has been suggested to be at the root of difficulties experienced by individuals with ASD (Just et al., 2004; 2012). However, observed atypical functional connectivity patterns in terms of face processing in individuals with ASD are inconsistent, with reviews suggesting both hypo- and hyperconnectivity between the core as well as the extended brain regions involved in the processing of neutral as well as expressive faces (Dichter, 2012; Nomi & Uddin, 2015). One study instructed adults with and without ASD to judge dynamic faces in terms of age or expression and found hypoconnectivity between the amygdala as well as the superior temporal sulcus and frontal regions in ASD, and between fusiform gyrus and occipital cortex (but only during expression judgements), while hyperconnectivity in ASD was observed between the fusiform and prefrontal cortex (Wicker et al., 2008). Another study in adults with and without ASD observed hypoconnectivity between the amygdala and fusiform gyrus during facial identity processing (Kleinhans et al., 2008). Hypoconnectivity between inferior frontal gyrus and fusiform gyrus was observed in a mixed-age group of adolescents and adults with and without ASD during a facial memory task (Koshino et al., 2008). In pre-adolescent children with ASD, hyperconnectivity was observed between amygdala and superior temporal sulcus as well as inferior frontal gyrus, but only during incongruent eye gaze trials (Murphy et al., 2012). One study showed hypoconnectivity to inverted faces between fusiform and inferior frontal regions in children with ASD compared to their neurotypical counterparts, a difference that was not observed in response to upright faces (Mamashli et al., 2021). Altogether, underconnectivity is found more often than hyperconnectivity, but precise patterns of atypical functional connectivity are rather dissimilar across studies, likely due to the heterogeneity of the ASD population and the use of different designs, tasks, and analysis approaches.

3.2.2. Results of studies using EEG

3.2.2.1. Classic EEG approaches: event-related potentials

EEG has often been used to study face processing in children and adults with ASD. The majority of studies using classic EEG approaches (such as event-related potentials or ERPs) has focused on the N170 component, which shows approximately 170 ms after the onset of a face stimulus over the occipito-temporal area (Bentin et al., 1996). Interestingly, the N170 component appears to display larger amplitudes to faces compared to non-face stimuli in neurotypicals (Bentin et al., 1996; Rossion et al., 2000). Another component that is often investigated in face processing studies is the P100 component, which is thought to reflect more basic sensory processes (Neuhaus et al., 2016). In ASD, results of studies investigating (expressive) faces in children and adults have yielded inconsistent results (Black et al., 2017; Kang et al., 2018; Monteiro et al., 2017).

Studies investigating facial identity processing found delayed latencies in the N170 component in children with ASD (Hileman et al., 2011; Webb et al., 2006). In adults with ASD, typical P100 and N170 latencies and amplitudes have been observed, in the absence of a behavioural inverted face effect in the ASD group (Webb et al., 2012). In contrast, atypical N170 latencies and amplitudes have been observed in adults with ASD combined with an intact behavioural face inversion effect (Tavares et al., 2016). A recent meta-analysis found N170 latencies to be significantly delayed in ASD compared to neurotypicals (Kang et al., 2018). However, this finding might reflect a more general slowness of processing in ASD, non-specific to faces (Vettori et al., 2018). Furthermore, an association between N170 latency and recognition memory of faces was observed, linking improved face recognition to longer N170 latencies in ASD and showing the opposite trend in neurotypicals (McPartland et al., 2004). This finding was interpreted to show that adults and adolescents with ASD need more time to recognise faces, as they are not experts at face processing.

Studies investigating facial emotion processing using EEG in children with and without ASD have shown delayed latencies in N170 (Batty et al., 2011) and P100 components (Batty et al., 2011), as well as smaller N170 (de Jong et al., 2008, Tye et al., 2014) and P100 amplitudes (Batty et al., 2011). Other studies did not show differences between children with and without ASD regarding latency and amplitude in N170 (Apicella et al., 2013) and P100 components (O'Connor et al., 2005; Wong et al., 2008). ERP studies investigating facial emotion processing in adults with ASD are scarce and have yielded ambiguous results. Findings show delayed N170 latencies (O'Connor et al., 2005, 2007), smaller N170

amplitudes and delayed P100 latencies (O'Connor et al., 2005) in adults with ASD, while other studies do not report differences between groups regarding amplitudes and latencies in N170 (Faja et al., 2016; Magnée et al., 2008; 2011; Tseng et al., 2015) and P100 components (Magnée et al., 2008).

3.2.2.2. A new approach to EEG

Recently, a new EEG approach - using a combination of *frequency-tagging and fast periodic visual stimulation (FPVS)* - was introduced in ASD research (for more information on FPVS, see Chapter 1 section 2.5). FPVS has been used to study facial identity in both adult and child populations with ASD. While atypical facial identity processing was observed in children with ASD (Vettori, Dzhelyova, et al., 2019), researchers did not find a significant difference between adults with and without self-reported ASD (Dwyer et al., 2019). Regarding facial expression processing, previous research has demonstrated an emotion-specific processing deficit in children with ASD. Researchers found that boys with ASD are less sensitive than neurotypical boys when detecting angry and fearful faces (Van der Donck et al., 2020). Thus far, no study applied this FPVS-EEG approach to investigate facial expression processing in adults with ASD.

3.3. Possible mechanisms of face processing difficulties in ASD

Several mechanisms have been proposed as to what could cause the face processing difficulties in individuals with ASD. Note that the proposed mechanisms are by no means mutually exclusive, nor exhaustive. Due to these - and most likely other - mechanisms, recognition of both facial identity and expression can become more challenging, which in turn can affect social functioning in individuals with ASD.

3.3.1. Reduced attention to faces

A first mechanism is proposed by Schultz (2005). He suggests that reduced attention for faces throughout development plays a role in face processing difficulties, as faces do not seem highly emotionally salient for individuals with ASD. More generally, it has been suggested that individuals with ASD have a severely diminished social motivation (Chevallier et al., 2012). An ASD-specific endogenous lack of attention to faces is suggested to drive the atypicalities in face processing, as behavioural difficulties and neural anomalies seem to disappear when the task involves familiar faces (Nomi & Uddin, 2015).

Furthermore, when oxytocin is administered, face-responsive brain activity normalises (Domes et al., 2013) and positive social behaviour increases (Kemp & Guastella, 2011), suggesting that the lack of attention may be due to an atypical social reward system (Nomi & Uddin, 2015).

3.3.2. Impaired holistic processing of faces

A second interpretation highlights impaired holistic processing to play a role in the difficulties to recognise faces (Richler & Gauthier, 2014). Research has shown that faces are typically processed holistically, meaning distinct facial features (e.g., eyes, mouth, nose) are not processed as independent parts but rather as an integrated whole (e.g., Rossion, 2013). These findings are based on the face inversion effect: expert face recognition abilities are disrupted when a face is turned upside down (Yin, 1969). Individuals with ASD are suggested to process faces less holistically compared to neurotypicals, which would make achieving expert levels of face recognition very challenging. However, evidence is mixed as to whether holistic processing of faces by individuals with ASD is actually impaired, as some studies show a reduced or absent face inversion effect (e.g., O'Brien et al., 2014; Vettori, Dzhelyova et al., 2019), while others found it to be unaffected (e.g., Hedley et al., 2015).

3.3.3. Eye avoidance

A third mechanism suggests the involvement of eye avoidance (Nomi & Uddin, 2015; Tanaka & Sung, 2016). Individuals with ASD tend to avoid looking at the eye region, instead relying on information from the mouth (Spezio et al., 2007). A possible reason is that a direct gaze is perceived as socially threatening by individuals with ASD (active avoidance theory: Kylliäinen & Hietanen, 2006; Richer, 1976) or because they lack the social interest to the eye region, due to an atypical social reward system (Birmingham et al., 2011). Hence, individuals with ASD lose information imbedded in the 'diagnostic' upper part of the face, making face recognition a lot more difficult. Moreover, based on the two accounts of eye avoidance (i.e., active avoidance and disinterest), different neural predictions can be made regarding differences between individuals with and without ASD. The amygdala could either be hyperactive in individuals with ASD to signal a threat in the active avoidance account, or hypo-active in the light of indifference toward social stimuli because of reduced social reward (Nomi & Uddin, 2015). Notwithstanding the popularity of this mechanism, reviews have found no consistent evidence of eye avoidance (Falck-Ytter & von Hofsten, 2011; Guillon et al., 2014).

Chapter 4

Understanding face processing in ASD using fMRI

Abstract

The ability to recognise faces and facial expressions is a common human talent. It has, however, been suggested to be impaired in individuals with autism spectrum disorder (ASD). The goal of this study was to compare the processing of facial identity and emotion between individuals with ASD and neurotypicals (NT).

Behavioural and functional magnetic resonance imaging (fMRI) data from 46 young adults (aged 17-23 years, N_{ASD} = 22, N_{NT} = 24) were analysed. During fMRI data acquisition, participants discriminated between short clips of a face transitioning from a neutral to an emotional expression. Stimuli included four identities and six emotions. We performed behavioural, univariate, multi-voxel, adaptation, and functional connectivity analyses to investigate potential group differences.

The ASD group did not differ from the NT group on behavioural identity and expression processing tasks. At the neural level, we found no differences in average neural activation, neural activation patterns and neural adaptation to faces in face-related brain regions. In terms of functional connectivity, we found that the amygdala seems to be more strongly connected to the inferior occipital cortex and V1 in individuals with ASD. Overall, the findings indicate that neural representations of facial identity and expression have a similar quality in individuals with and without ASD, but some regions containing these representations are connected differently in the extended face processing network.

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1. Introduction

1.1. Face processing

Face processing is a crucial, extensively used human skill. Most people are experts in face recognition and can distinguish extraordinarily well between different facial identities and expressions (Tanaka, 2001; Tanaka & Gauthier, 1997). Nevertheless, individuals with autism spectrum disorder (ASD) are characterised by atypical verbal and non-verbal social communication, in which face processing plays an important role. Individuals with ASD may exhibit difficulties in both facial identity processing (i.e., struggling to recognise someone based on facial features) and facial emotion processing (i.e., struggling to recognise and interpret facial expressions) (Barton et al., 2004). These difficulties have been proposed to belong to the core deficits of ASD (Dawson et al., 2005; Schultz, 2005; Tanaka & Sung, 2016), even underlying the characteristic social difficulties of individuals with ASD (Dawson et al., 2005; Nomi & Uddin, 2015; Schultz, 2005).

However, when tested experimentally, the empirical evidence for atypicalities in facial identity processing in ASD is mixed. Reviews conclude that individuals with ASD generally – but not consistently - differ from neurotypical controls in terms of identity processing on a quantitative level (i.e., how well facial identity is discriminated), especially in adults. However, they disagree on whether there are also qualitative differences between the groups (i.e., use of different strategies for identity recognition) (Tang et al., 2015; Weigelt et al., 2012). Weigelt and colleagues (2012) conclude that individuals with ASD have a specific difficulty remembering faces, based on the finding that differences between groups are more likely to show up in studies that present facial stimuli consecutively (i.e., not simultaneously).

Likewise, the empirical evidence regarding difficulties in facial expression processing is mixed, in particular when considering basic emotions. Some studies suggest general problems with all emotions, others find specific difficulties (e.g., for one particular emotion, only for negative emotions, or only for especially complex emotions, but not for others), and other studies do not find differences at all (Harms et al., 2010; Uljarevic & Hamilton, 2013).

1.2. Neural basis of face perception

The literature on the neural basis of face perception is extensive. An influential neural model has been suggested by Haxby and colleagues (Haxby, Hoffman, et al., 2000). In this model, invariant facial features play an important role in identity recognition, while variant facial features aid social communication (e.g., understanding what someone is feeling based on the facial expression). The authors propose a hierarchical model mediating face perception, comprising a core system and an extended system. In the core model, the early perception of faces is carried out by inferior occipital regions (e.g., the occipital face area, OFA). In turn, this region provides input to the fusiform gyrus and the superior temporal cortex. Processing of invariant facial features (~identity) is associated with stronger activity in inferior temporal (fusiform) and inferior occipital regions (Kanwisher & Yovel, 2006). On the other hand, changeable aspects of the face (~expression) are processed by the superior temporal cortex (Hoffman & Haxby, 2000; Puce et al., 1998; Wicker et al., 1998). More recent work has suggested a higher degree of overlap between identity and emotion processing. More specifically, it has been shown that the superior temporal cortex responds to identity (e.g., Dobs et al., 2018; Fox et al., 2011) and the fusiform gyrus is activated while processing expressions (e.g., LaBar et al., 2003; Schultz & Pilz, 2009). Some studies even suggest facilitatory interactions between identity and emotion processing (e.g., Andrews & Ewbank, 2004; Calder & Young, 2005; Winston et al., 2004; Yankouskaya et al., 2017).

The three-region core network is complemented by an extended brain network aiding the further processing and interpretation of visual facial information (Haxby et al., 2002). For instance, the anterior temporal cortex has been implicated for biographical knowledge as a part of identity processing (Gorno-Tempini et al., 1998; Leveroni et al., 2000). Furthermore, the amygdala and the inferior frontal cortex play a crucial role in the processing of emotion (Adolphs & Tranel, 1999; Brothers, 1990; Haxby, Petit, et al., 2000; Sprengelmeyer et al., 1998).

Importantly, Haxby and colleagues emphasise that effective face processing can only be accomplished by the coordinated interaction and collaboration between several brain regions. The idea of multiple brain regions jointly collaborating in a face processing network has also been supported by other authors (e.g., Ishai, 2008; Tovée, 1998; Zhen et al., 2013). In addition, Nomi and Uddin (2015) highlight the importance of studying distributed neural networks to understand atypical face perception in ASD.

1.3. Neural face processing in ASD across methods

In this paper, we investigated how the neural processing of faces differs between individuals with and without ASD. For this purpose, we used different methods of analysis. Group differences in face processing between individuals with ASD and neurotypicals (NTs) have been investigated in previous neuroimaging studies.

First, a myriad of studies has compared the neural activity level of individuals with and without ASD. Reviews show that the inferior occipital gyrus, the fusiform gyrus, the superior temporal sulcus, the amygdala, and the inferior frontal gyrus have been found to be less active in individuals with ASD when looking at faces (Di Martino et al., 2009; Dichter, 2012; Nomi & Uddin, 2015; Philip et al., 2012). Studies specific to identity recognition have shown hypo-active inferior frontal and posterior temporal cortices in individuals with ASD (Koshino et al., 2008). Regarding expressive faces, reviews and meta-analyses show that the fusiform gyrus, the superior temporal sulcus, and the amygdala are less active in individuals with ASD (Aoki et al., 2015; Di Martino et al., 2009; Dichter, 2012; Nomi & Uddin, 2015; Philip et al., 2012).

Second, the literature pertaining neural representations characterising facial identity and facial expression processing in ASD is sparse. In the last decade, there has been an exponential growth of studies investigating the properties of neural representations through multivariate methods. These methods are known under names such as multi-voxel pattern analysis (MVPA), brain decoding, and representational similarity analysis (RSA) (Haynes & Rees, 2006; Kriegeskorte et al., 2008; Norman et al., 2006). It has been suggested that this approach offers a more sensitive measure to pinpoint how information is represented in the brain, compared to univariate analyses (Haxby et al., 2001; Koster-Hale et al., 2013). Multivariate methods have indeed been applied successfully to assess properties of face representations in neurotypicals (Goesaert & Op de Beeck, 2013; Kriegeskorte et al., 2007; Nemrodov et al., 2019; Nestor et al., 2011), and to compare and distinguish representations between ASD and NT groups in other domains (Gilbert et al., 2009; Koster-Hale et al., 2013; Lee Masson et al., 2019; Pegado et al., 2020). Strikingly, however, multivariate approaches have rarely been used to study face processing in the ASD population. One study performed MVPA to study facial emotion processing using dynamic facial stimuli, finding no differences between individuals with and without ASD (Kliemann et al., 2018).

Third, pertaining adaptation to faces in ASD, literature is again sparse. One study found that individuals with ASD show reduced neural adaptation to neutral faces in the fusiform gyrus (Ewbank et al., 2017). In addition, reduced neural habituation to neutral faces (Kleinhans et al., 2009; Swartz et al., 2013) and sad faces (Swartz et al., 2013) in the amygdala has been observed in individuals with ASD. This suggests that the processing of repeated face presentations occurs differently in individuals with ASD.

Finally, observed atypical functional connectivity patterns in individuals with ASD are inconsistent (Kleinhans et al., 2008; Koshino et al., 2008; Murphy et al., 2012; Wicker et al., 2008). Indeed, reviews suggest both hypo- and hyperconnectivity between the core as well as the extended brain regions involved in the perception of neutral as well as expressive faces (Dichter, 2012; Nomi & Uddin, 2015)

1.4. Current study

Many studies have investigated face processing in autism, but the methodological approach is generally diffuse and scattered. For instance, studies involving only identity processing or only emotion processing, only behavioural processing, or only neural processing, or involving only a selective and particular analysis approach. This fragmented approach has yielded inconsistent and scattered findings. With the present study, we aimed to offer an integrative picture of face processing abilities in ASD. For this purpose, we complemented a very comprehensive battery of behavioural face processing tasks with one of the most comprehensive series of fMRI analyses involving univariate, multivariate, adaptation, and functional connectivity analyses.

In this study, young adults with ASD and age- and IQ matched neurotypicals performed behavioural face processing tasks outside of the scanner. In addition, they performed a one-back task with dynamic facial stimuli while fMRI data was acquired. The stimuli, presented in a variable block design, displayed a face changing from a neutral to an emotional expression. The fMRI analyses included (1) a univariate analysis to study brain activity levels along the face processing network, (2) multi-voxel pattern analysis (MVPA) to assess the quality of neural representations of identity and expression, (3) release from adaptation to the repetition of facial identity and/or expression, and (4) functional connectivity among the core and extended face processing network.

Based on the large body of literature, especially given the use of dynamic facial stimuli, we expected to find differences between the groups. Behaviourally, we expected to observe

poorer face processing performance, especially in tasks involving a memory component and impeding the use of perceptual matching strategies. At a univariate level, we expected to find differences between the groups. Due to the large inconsistencies in the literature, we made no a priori predictions about the regions of interest in which we would observe these differences. At a multivariate level, due to the sparseness of previous studies in ASD, we made no strong a priori predictions. Yet, based on the model of Haxby and colleagues (Haxby, Hoffman, et al., 2000), we expected that facial identities would be more robustly decoded from neural responses in the inferior occipital cortex, the fusiform gyrus, and the anterior temporal cortex. On the other hand, we expected facial expressions to be more reliably decoded from neural responses in the superior temporal cortex, the amygdala, and the inferior frontal cortex. Regarding the release from adaptation, we again had no strong a priori predictions due to the sparseness of studies in ASD. Since the inferior occipital cortex and the amygdala were implicated in previous studies, we expected potential group differences to show up in those regions. Here, again, we expected different anatomical regions to be differently involved in facial identity versus expression processing. Finally, regarding functional connectivity among the face network, we expected to find atypical functional connectivity patterns in the ASD group, most likely involving hypoconnectivity in the ASD group. However, we made no strong predictions due to the largely inconsistent findings in the literature.

2. Methods

2.1. Participants

Fifty-two young adults participated in this study (all male, ages 17-23 years), including 27 men with a formal ASD diagnosis and 25 age-, gender-, and IQ-matched neurotypical (NT) participants. Participants, and participants' parents when the participant was under 18, completed informed consent prior to scanning. The study was approved by the Medical Ethics committee of the University Hospital Leuven (UZ Leuven).

Participants with ASD were diagnosed by a multidisciplinary team following DSM-IV or DSM-5 criteria. They were diagnosed and recruited through the Autism Expertise Centre and the Psychiatric Clinic at the University Hospital Leuven. None of the participants with ASD had comorbid neurological, psychiatric, or genetic conditions. Neurotypical adults were recruited through online advertising. None of the NT participants, nor first degree relatives, had a history of neurological, psychiatric, or medical conditions known to affect brain structure or function. None of the participants took psychotropic medication. All participants had normal or corrected-to-normal vision, and an IQ above 80. Participants generally showed an above average intelligence, resulting in an ASD group consisting of mainly high functioning individuals with ASD. In addition, participants with ASD showed high levels of social adaptive functioning (e.g., most attend high school or higher education, or have a regular job).

Due to a range of problems during acquisition (technical or instructional difficulties; too much motion, see later sections), six participants were excluded from all analyses. Five of the excluded participants were part of the ASD group. Hence, analyses were ultimately run on 46 (22 ASD and 24 NT) participants.

2.2. IQ, screening questionnaires and matching

Intelligence quotient (IQ) was measured using the following subtests of the Wechsler Adult Intelligence Scale (WAIS-IV-NL): block design, similarities, digit span, vocabulary, symbol search, and picture completion, allowing the computation of verbal, performance, and full-scale IQ (Table 4.1). In addition, a Dutch version of the Social Responsiveness Scale for

adults (Constantino & Todd, 2005; Noens et al., 2012) was completed both by participants and at least one significant other (mother, father, sister, or partner). The SRS is a tool to assess autistic traits in adults. Reported scores are t-scores, ranging from 20 (very high level of social responsiveness) to 80 (severe deficits in social responsiveness). Thus, the higher the t-score, the more autistic traits are present. In contrast to other measures, a difference in SRS-scores between the groups was expected. Finally, to rule out differences between the groups regarding depression and anxiety, participants completed a Dutch version of the Beck Depression Inventory (BDI-II-NL) (Beck et al., 1996; Van der Does, 2002) and a Dutch version of the Spielberger State-Trait Anxiety Inventory (ZBV) (Van der Ploeg, 1980).

Table 4.1. Participant characteristics of ASD group (N_{ASD} = 22) and NT group (N_{NT} = 24)

	ASD				NT				Difference	
	Mean	Min	Max	SD	Mean	Min	Max	SD	T	p
Age	19.18	17	23	1.82	20.08	17	23	1.98	1.61	.1154
Verbal IQ	113.95	98	134	10.49	113.29	90	140	13.41	0.19	.8536
Performance IQ	114.45	81	153	16.61	111.54	85	141	16.47	0.60	.5537
Full scale IQ	111.86	89	147	13.07	111.67	87	143	14.48	0.73	.4702
BDI-II-NL	8.05	0	23	6.25	4.83	0	21	5.92	1.79	.0803
STAI State	32.82	20	50	6.94	31.58	24	42	5.79	0.66	.5145
STAI Trait	38.18	23	62	9.99	33.71	22	53	8.25	1.66	.1037
SRS self	58.45	42	77	10.25	48.21	36	61	7.67	3.86	**.0004**
SRS other	63.68	46	87	11.06	44.25	20	69	9.05	6.55	**< .0001**

Note. Abbreviations. BDI: Beck Depression Questionnaire. STAI: State-Trait Anxiety Inventory. SRS: Social Responsiveness Scale.

NT participants were recruited to match ASD participants, which was largely successful (see Table 4.1). We found no significant differences between the ASD group and the NT group regarding a range of control measures. As expected, scores on the SRS differed significantly between the groups. Both for the self-report and for the other-report version of the SRS questionnaire, individuals with ASD scored significantly higher than NTs. Interestingly, we found an interaction between informant (i.e., the person who filled out the SRS-scale) and group ($F_{1,44}$ = 5.23, p = 0.0270): individuals with ASD scored lower (i.e.,

more socially adaptive) when filling out the questionnaire themselves, whereas the opposite trend emerged in the control group.

2.3. Behavioural data acquisition

Participants performed several behavioural face processing tests, selected to avoid low-level perceptual strategies and to probe face memory abilities. The Benton Face Recognition Test (BFRT) (Benton et al., 1983) was used to assess the ability to recognise individual faces. The Cambridge Face Memory Test (CFMT) (Duchaine & Nakayama, 2006) was used to assess the ability to remember individual faces. The Emotion Recognition task (ERT) (Kessels et al., 2014; Montagne et al., 2007) and the Emotion Recognition Index (ERI) (Scherer & Scherer, 2011) were used to assess the ability to recognise facial emotions.

We used a digitised version of the BFRT (BFRT-c) (Rossion & Michel, 2018). This test required participants to match facial identities despite changes in lighting, viewpoint, and size, preventing them from relying on a low-level pixel-matching strategy. The test comprised a total of 22 trials. In every trial, four grayscale photographs were presented on the screen. In the upper part of the screen, a test face was presented, while in the lower part three faces were displayed: one target face and two distractor faces. Participants were instructed to select which of the three 'lower' faces had the same identity as the test face. Test, target, and distractor stimuli were shown simultaneously to minimise the memory load.

The CFMT also required participants to match faces across viewpoints and levels of illumination. However, this test did involve a memory component. Furthermore, the test consisted of three stages. In the first stage, three study images of the same face were presented subsequently for three seconds: frontal, left and right viewpoint. Then, three faces were displayed, comprising one of the three study images and two distractor images. Participants were instructed to select the target identity, i.e., the identity they recognised from the study images. In the second stage, participants received the same instructions, but had to generalise the identity to a novel image, as the target image was different from the study images (i.e., a novel image of the same identity in which the illumination and/or pose varied). In the third stage, noise on the images added an extra level of difficulty to the task. The test comprised 72 items: 18 items in the first stage, 30 items in the second stage, 24 items in the third stage.

The ERT allowed us to investigate the explicit recognition of six dynamic facial expressions (i.e., anger, fear, happiness, sadness, disgust, surprise). Short video clips were presented, displaying a dynamic face in front view. These dynamic faces changed from a neutral to an emotional expression at either 40, 60, 80 or 100% intensity of the expression. Participants were instructed to select the corresponding emotion from six written labels displayed on the screen. Each intensity level comprised 24 trials, resulting in a total of 96 trials.

The ERI was also used to investigate the ability to recognise emotions. Pictures of posed expressions were presented for three seconds. Participants were instructed to select which emotion was expressed in the picture by clicking the correct label. The test included more items for difficult emotions (i.e., sadness, fear, anger) and relatively fewer items for easily recognisable emotions (happiness, disgust), with a total of 30 trials.

2.4. fMRI data acquisition

2.4.1. Stimuli

Stimuli were taken from the Emotion Recognition Task (ERT) (Kessels et al., 2014; Montagne et al., 2007). They consisted of 24 two-second video clips in which a face slowly transitioned from a neutral to a 100% expressive emotional face, while keeping identity constant (Figure 4.1). Six 'basic' (Ekman & Cordaro, 2011) facial expressions were included: anger, disgust, fear, happiness, sadness, and surprise. Each emotion was expressed by four different individuals: all Caucasian, two male and two female identities. All possible combinations between the four identities and six emotions resulted in twenty-four dynamic face stimuli.

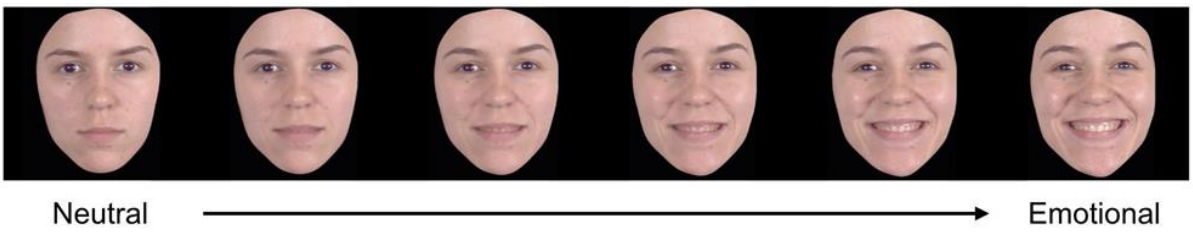

Figure 4.1. Example of dynamic stimulus presented in the scanner. Faces gradually transitioned from a neutral to an emotional facial expression (happy in this case).

Stimuli were generated by morphing two static pictures: one showing a neutral and one showing an emotional facial expression. These stimuli were first constructed by Montagne and colleagues (2007) and used in previous (behavioural) research (Evers et al., 2015; Poljac et al., 2013). In addition, the same stimuli were already used during behavioural testing, in the Emotion Recognition Task, with the difference that we only used the clips transitioning from a neutral to a 100% expressive facial expression for fMRI data acquisition.

2.4.2. Design

The fMRI experiment followed a design with short blocks of variable lengths. Every run lasted 270 seconds and consisted of two two-minute periods of stimulus presentation. Stimulus presentation was preceded and followed by a ten-second fixation block (Figure 4.2). Every two-minute period of stimulus presentation contained 60 trials shown in 24 blocks: one block per stimulus condition. These 24 blocks had variable lengths: every stimulus was shown for either one, two, three, or four consecutive trials. Therefore, as every stimulus lasted for two seconds, the length of every block varied between two and eight seconds.

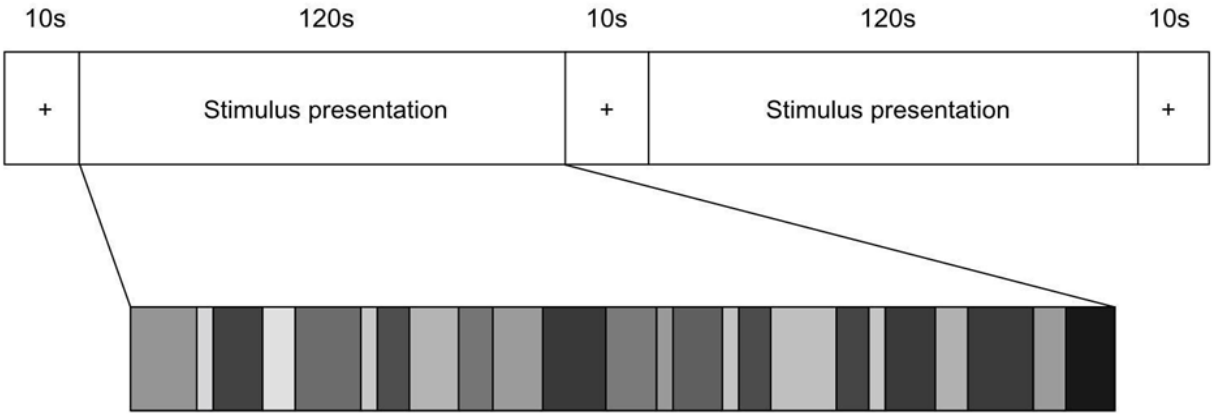

Figure 4.2. Design of one run. Ten seconds of fixation alternated by two two-minute periods of stimulus presentation. Within a two-minute period of stimulus presentation, all 24 stimuli were shown at least once, in blocks of different lengths (2-8 seconds).

In this study, we used a design with short trials, variable block lengths and no inter-stimulus intervals. This kind of design is based on the 'continuous carry-over design' proposed and used by Aguirre (2007). A very similar design has previously been used in our research group (Bulthé et al., 2014, 2015)

Participants performed a change detection task in which identity and emotion processing were integrated. They were instructed to press a button whenever the current stimulus differed from the previous one, regardless of the change occurring in identity or emotion. This one-back task ensured that participants were looking at the stimuli and paying attention to both identity and facial expression. Six up to twelve runs were acquired for each participant, depending on the length of scanning that was comfortable for a participant. We found a marginally significant difference in the number of acquired runs between the ASD group ($mean_{ASD}$ = 9.64 runs) and the NT group ($mean_{NT}$ = 10.54 runs) (Mann-Whitney U test; W = 345, p = 0.0494).

2.4.3. fMRI data acquisition

fMRI data were collected using a 3T Philips Ingenia CX scanner, with a 32-channel head coil, using a T2*-weighted echo-planar (EPI) pulse sequence (52 slices in a transverse orientation, FOV = 210 x 210 x 140 mm, reconstructed in–plane resolution = 2.19 x 2.19 mm, slice thickness = 2.5 mm, interslice gap = 0.2 mm, repetition time (TR) = 3000 ms, echo time (TE) = 30 ms, flip angle = 90 degrees). In addition, a T1-weighted anatomical scan was acquired from every participant (182 sagittal slices, FOV = 250 x 250 x 218 mm, resolution = 0.98 x 0.98 x 1.2 mm, slice thickness = 1.2 mm, no interslice gap, repetition time (TR) = 9.6 ms, echo time (TE) = 4.6 ms).

2.5. Analyses

2.5.1. Behavioural analyses

For each of the face processing tasks, we analysed the reaction times and accuracy with repeated measures ANOVA using the Afex package v0.22-1 (Singmann et al., 2018) in R v3.4.3 (R Development Core Team, 2012). 'Accuracy' and 'Reaction time' were included as dependent variables, and 'Group' (NT vs. ASD) as a between-subject factor. For the analysis of the CFMT, we additionally included the different stages of the test (intro, no noise and noise) as a within-subject factor. For analyses of reaction times, only correct trials were

considered. When the data did not meet the assumption of normally distributed residuals, we performed a square root transformation on the data.

In addition to the face processing tasks, we analysed accuracy and reaction times on the task performed during fMRI data acquisition using custom code in MATLAB. Due to technical problems, responses failed to (reliably) register in all runs of five participants (three ASD and two NT), and in at least one run of eight other participants. These runs were excluded from further behavioural analyses.

2.5.2. fMRI analyses

2.5.2.1. fMRI pre-processing

Data were pre-processed using MATLAB with the Statistical Parametric Mapping software (SPM 8, Wellcome Department of Cognitive Neurology, London). First, functional scans were corrected for differences in slice timing. Second, the slice-timing-corrected scans were realigned to a mean scan per subject to correct for motion. The six motion parameters obtained during this process were used (1) as confounds in the general linear model, and (2) to check for excessive head motion, a priori defined as scan-to-scan movement exceeding one voxel in either direction (three participants excluded: two individuals with ASD, one NT) (cf. Bulthé et al., 2019; Pegado et al., 2018; Peters et al., 2016; Van Meel et al., 2019). Third, anatomical scans were co-registered with the slice-timing-corrected and realigned functional scans. Fourth, the anatomical and functional scans were normalised, resampling the scans to a voxel size of 2.5 x 2.5 x 2.5 mm. Finally, slice-timing-corrected, realigned, co-registered and normalised functional images were spatially smoothed with a Gaussian kernel with a full-width half maximum (FWHM) of 5mm.

2.5.2.2. fMRI statistics

The BOLD response for each run was modelled using a general linear model (GLM). We constructed two different GLMs using different conditions for (1) the univariate, multivariate and functional connectivity analyses and (2) the adaptation analysis. In both approaches, we followed the logic of the continuous carry-over design proposed by Aguirre (2007).

In the first approach, the responses to individual stimuli are referred to as 'direct effects' (Aguirre, 2007). In this general linear model, the onset and duration of each stimulus block (i.e., a face with a particular identity and particular expression) were utilised to capture the

signal for one specific condition. Therefore, the GLM contained 24 regressors of interest (one for each condition, i.e., every stimulus) and six motion correction parameters per run. As a result, we obtained a beta-value for every condition (every stimulus), and for the six regressors accounting for head motion. Estimation of the GLM resulted in beta-values. These beta-values were used during the univariate, multivariate and functional connectivity analyses.

We used a different approach to model the adaptation effects, referred to as 'indirect effects' or 'carry-over effects' (Aguirre, 2007). Instead of regressors referring to individual conditions (as in the first approach), the regressors in this model refer to the relationship between the conditions (i.e., relation between stimuli). More specifically, we modelled four adaptation conditions to classify the relationship between the 24 original conditions (i.e., 24 stimuli). Trials were assigned to the 'AllSame'-condition when the current stimulus was a repetition of the previous stimulus (72 trials per run). When the current stimulus had the same identity but a different emotion than the previous one, the trial was labelled 'DiffEmo' (10-14 trials per run). When the emotional expression was repeated but the identity changed, the trial was assigned to the 'DiffId'-condition (10-14 trials per run). Finally, if both identity and emotion were different in the current trial compared to the previous one, the trial was labelled 'AllDiff' (22-26 trials per run). Additionally, to account for the presence of fixation trials, we introduced two more conditions. The first trial of stimulus presentation after a fixation trial was assigned to the 'FixtoStim' condition. Fixation trials themselves were labelled 'Fix'. This resulted in a total of six conditions for the adaptation analysis. For every participant, a GLM was estimated using the onsets and durations of the newly defined adaptation conditions. Accordingly, the GLM consisted of 12 regressors per run: six regressors of interest (the six conditions described above) and six motion correction parameters. Estimation of the GLM resulted in beta-values. These were used during the adaptation analysis.

2.5.2.3. Regions of interest

Next, we defined our regions of interest (ROIs). We included seven ROIs comprising the network of regions mostly involved in face processing. First, the regions that are typically considered the core face-selective regions, i.e., the inferior occipital cortex (including the occipital face area 'OFA'), the posterior fusiform cortex (including the fusiform face area 'FFA'), and the superior temporal cortex (including the superior temporal sulcus 'STS'). Next, the regions that are often considered as the extended face network, i.e., the

amygdala, the anterior temporal cortex (including the temporal pole), and the inferior frontal cortex (including the orbitofrontal cortex). Finally, the region where visual information enters the cortex, i.e., V1. The relevance of these regions is supported by a large literature (e.g., Adolphs, 2008; Avidan et al., 2014; Hoffman & Haxby, 2000; Ishai, 2008; Kanwisher et al., 1997; Pitcher et al., 2011; Rotshtein et al., 2005). Apart from V1, this network is also activated in the automated brain mapping database Neurosynth when searching for terms such as 'faces' and 'facial expressions'.

Next, we created masks for these ROIs. As all the intended regions were incorporated in WFU PickAtlas' 'aal', we used this atlas to delineate anatomical masks. We incorporated potential inter-subject variability by dilating all masks 3-dimensionally with 1 voxel, restricted to the lobe they belonged to. After defining and inspecting the anatomical masks, we decided to merge the (very large) fusiform gyrus with the temporal pole, and re-divide them in a posterior fusiform mask (encompassing the FFA) and a larger anterior temporal mask (including the temporal pole). We partitioned the merged mask along Y-coordinate 50 in a standard (91x109x91) space, based on literature (Grill-spector et al., 2004; Spiridon et al., 2006; Summerfield et al., 2008), and visually ensured that the FFA resided in the posterior fusiform mask. In addition, we used existing face parcels of the FFA, OFA and STS (Julian et al., 2012) to confirm that these regions were situated within the posterior fusiform, the inferior occipital and the superior temporal masks, respectively.

We ensured that all masks were mutually exclusive by deleting all overlapping voxels. Anatomical masks were co-registered to a functional scan (fully pre-processed except for smoothing) to bring them in the same space as the pre-processed images (63x76x55). Finally, the anatomical masks were functionally restricted by computing the intersection with the face-responsive voxels. For this purpose, we used a whole-brain second level "all versus fixation" contrast across all participants. This contrast map was similar to probabilistic maps of face sensitive regions (Engell & McCarthy, 2013). Our "all versus fixation" contrast map was thresholded at $p < .005$, uncorrected. With this threshold, the smallest ROI contained 174 voxels, which was large enough to eventually allow the reduction of all ROIs to this size. Table 4.2 depicts the number of voxels in each ROI, both for the purely anatomical masks and for the functionally restricted masks. Figure 4.3 shows the final ROIs, after functional restriction thresholded at $p < .005$ uncorrected.

Table 4.2. Number of voxels in the purely anatomical and in the functionally restricted masks with a threshold of $p < .005$ uncorrected

	# voxels anatomical	# voxels after restriction
Inferior Occipital	1473	1364
Posterior Fusiform	3222	1384
Superior Temporal	3586	563
Amygdala	639	258
Anterior Temporal	3969	174
Inferior Frontal	7608	381
V1	2249	710

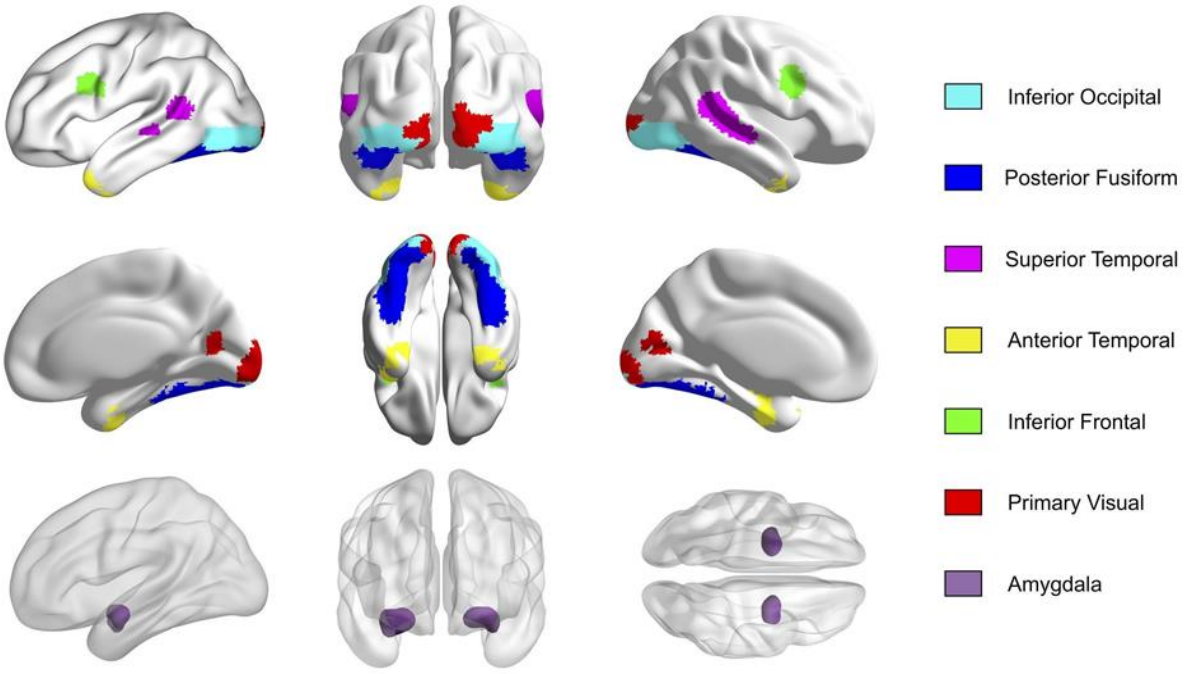

Figure 4.3. Regions of interest after functional restriction thresholded at $p < .005$, uncorrected. The top and middle row display the six cortical regions of interest, the bottom row shows the single subcortical region in this study: the amygdala.

2.5.2.4. Univariate analyses

We conducted an ROI-based univariate analysis using custom code in MATLAB. For every participant, the average beta-value across all runs was computed for the "all versus fixation" contrast. These values were used in a two-sample t-test to test for group differences. We corrected for multiple comparisons by controlling the false discovery rate (FDR) with $q < 0.05$ (Benjamini & Hochberg, 1995). Below, we will use the term 'activation' to refer to average beta-values.

2.5.2.5. Multivariate analyses

The multivariate analysis involved an ROI-based decoding analysis, performed in MATLAB using custom code and the LIBSVM toolbox (Chang & Lin, 2011). The classification was conducted using support vector machines (SVM) with the default parameters of the LIBSVM toolbox. The code was very similar to the code made available by Bulthé and colleagues (2019). To make sure that the size of the ROIs was not driving the decoding results, we redefined all ROIs to have an identical number of voxels, equal to the number of voxels in the smallest ROI (i.e., the anterior temporal cortex). Accordingly, we randomly selected 174 voxels from the bigger ROIs to define these new equally sized ROIs.

The fMRI activity profiles (t-maps) in every ROI were used as input for an SVM-based decoding classification. First, we extracted response patterns for each stimulus condition, corresponding to a list containing the t-values of all voxels in the region. We did this separately for every subject, every ROI and for each run. These patterns were standardised to have a mean of zero and a standard deviation of 1 across all voxels within an ROI. Subsequently, a repeated random subsampling cross-validation procedure was used, in which the data were randomly assigned to either the training set (70% of the data), or the test set (30% of the data). This subsampling occurred 100 times. We trained the SVM to pairwisely distinguish all 24 conditions (four identities and six emotions), acquiring decoding accuracies for all 276 combinations in every ROI and for every subject. To obtain decoding accuracies for identity in every ROI, we computed the average decoding accuracy across all combinations that included different identities while emotion remained stable (e.g., happy identity 1 versus happy identity 2, sad identity 2 versus sad identity 4). We acquired decoding accuracies for emotion in every ROI by calculating the average decoding accuracy of all combinations that included different expressions, while identity stayed the same (e.g., happy identity 1 versus sad identity 1, sad identity 3 versus surprise

identity 3). Using a two-tailed one sample t-test, we tested whether decoding accuracy significantly differed from chance level (0.5). We tested group differences for both identity-decoding and emotion-decoding with a two-sample t-test and corrected for multiple comparisons by controlling for the false discovery rate (FDR, $q < .05$) (Benjamini & Hochberg, 1995). In addition, we checked for an interaction between ROI and condition (identity versus emotion). For this purpose, we performed a repeated measures ANOVA with 'Decoding accuracy' as the dependent variable, 'Group' as between-subject factor, and 'Condition' (identity, emotion) and 'ROI' as within-subject factors.

2.5.2.6. Adaptation analysis

For this analysis, data were processed using MATLAB with the Statistical Parametric Mapping software (SPM12, Wellcome Department of Cognitive Neurology, London). To assess possible differences in adaptation to faces between ASD and NT participants, we constructed a different GLM, as described in section 2.5.3. fMRI statistics.

We ran an ROI-based analysis, in which an average (across voxels) beta-value was computed for every adaptation condition, in every participant within every ROI. The same ROIs as in the univariate analysis were used. Based on the average beta-values in every ROI, we calculated three adaptation indices to capture the release from adaptation. As a first step, we subtracted the average beta-value in the 'AllSame' condition (baseline) from the average beta-value in the three conditions of interest (i.e., 'AllDiff', 'DiffId', 'DiffEmo'). This resulted in three adaptation values ('AllDiff-AllSame', 'DiffId-AllSame', 'DiffEmo-AllSame') for every participant in every ROI. Subsequently, we computed the average adaptation indices for every group within every ROI. To assess whether the adaptation indices were significantly different from zero – thus showing a significant release from adaptation - a two-sided one-sample t-test was applied. In addition, a two-sample t-test allowed us to assess differences in adaptation indices between the two groups. Below, we will use the term 'activation' to refer to average beta-values.

2.5.2.7. Functional connectivity analysis

We investigated intrinsic functional connectivity by looking at correlations between temporal fluctuations in the BOLD signal across ROIs. These fluctuations represent neuronal activity organised into structured spatiotemporal profiles, reflecting the functional architecture of the brain. It is generally believed that the level of co-activation of

anatomically separated brain regions reflects functional communication among these regions (Gillebert & Mantini, 2013). Intrinsic functional connectivity is typically studied in resting-state data but can also be investigated based on task-related data. However, for the latter, an additional pre-processing step is necessary to subtract the contribution of the stimulus-evoked BOLD response (Fair et al., 2007; Gillebert & Mantini, 2013). This approach was used here.

The functional connectivity analysis was adapted from previous work, used both within our research group (Boets et al., 2013; Bulthé et al., 2019; Pegado et al., 2020; Van Meel et al., 2019) and elsewhere (e.g., King et al., 2018). As done before, several additional pre-processing steps were performed on the already pre-processed (but non-smoothed) data: regression of head motion parameters (and their first derivatives), regression of signals from cerebrospinal fluid (i.e., ventricles) and white matter (and their first derivatives), bandpass filtering between 0.01 and 0.2 Hz (Balsters et al., 2016; Baria et al., 2013), and spatial smoothing at 5mm FWHM. Finally, regression of stimulus-related fluctuations in the BOLD response was performed by including 24 regressors corresponding to the timing of the presented stimuli (Boets et al., 2013; Ebisch et al., 2013; Fair et al., 2007; Gillebert & Mantini, 2013).

Seed regions included in this functional connectivity analysis were the same seven, equally sized regions as included in the multivariate analysis. Within each ROI, an average BOLD time course was calculated across all voxels in that region. In a next step, we used these averaged BOLD time courses to obtain a functional connectivity matrix for every subject. More specifically, we computed Pearson cross-correlations between the BOLD time courses of all pairs of ROIs. These matrices were then transformed to Z-scores using a Fisher's r-to-Z transformation. Next, group-level functional connectivity matrices were calculated by performing a random-effects analysis across subjects with a p_{FDR} thresholded at 0.001. Finally, to compare the functional connectivity values between the two groups, we conducted two-sample t-tests on the group-level functional connectivity matrices, p_{FDR} thresholded at 0.05.

3. Results

3.1. Behavioural results

Accuracy and reaction times on the behavioural tasks were examined using group (NT vs. ASD) as a between-subject factor. For the CFMT, the different stages of the test (intro, no noise and noise) were added as a within-subject factor. Results are displayed in Table 4.3. Generally, across all tasks, there were no significant main effects of group for accuracy or reaction times. Both groups performed equally well and fast on the Emotion Recognition Index (ERI), the Emotion Recognition Task (ERT), and the Benton Face Recognition Task (BFRT). Analysis of the Cambridge Face Memory Test (CFMT) revealed that there was no significant effect of group on accuracy or on reaction times. The interaction between group and test phase was not significant for the accuracy, nor for the reaction times. Post hoc comparisons between groups in the different stages of the CFMT confirmed that significant group differences were observed in neither of the three stages.

Table 4.3. Results of behavioural analyses.

		ASD		NT		Difference		
		Mean	SD	Mean	SD	df_1, df_2	F	p
ERI	ACC (%)	69.2	3.2	70.6	3.9	1,44	0.62	.44
	RT (s)	1.9	1.9	1.7	1.6	1,44	3.28	.08
ERT	ACC (%)	61.6	11.5	60.7	10	1,44	0.11	.74
	RT (s)	2.0	2.1	1.9	1.9	1,44	1.93	.17
BFRT	ACC (%)	80.3	10.5	82.1	7.5	1,44	1.39	.25
	RT (s)	11.8	3.3	10.5	5.8	1,44	1.14	.29
CFMT	Total ACC (%)	65.2	15.0	69.1	14.3	1,44	1.08	.31
	Total RT (s)	4.1	4.4	3.9	2.9	1,44	0.02	.90

Accuracy and reaction times of the task in the scanner were examined and compared between groups. For analyses of accuracy, both correct responses and correct non-responses were considered. Both groups performed equally well ($mean_{ASD}$= 92.67%, $mean_{NT}$= 93.70%; t_{44} = 0.79, p = 0.43) and equally fast ($mean_{ASD}$= 1.01s, $mean_{NT}$= 1.00s; t_{38} = 0.18, p = 0.86). These results are consistent with the results of the ERT completed outside of the scanner. The high scores suggest that the task was rather easy and that it served its purpose of keeping participants' attention on the stimuli.

3.2. Univariate fMRI results: neural activation while watching faces

We performed ROI-based univariate analyses to investigate the average levels of activation within the ROIs, and whether these differed between the groups. Results of the ROI-based univariate "all versus fixation" analysis are depicted in Figure 4.4, displaying average neural activation levels while participants were watching faces. We found no significant difference in neural activation between the ASD group and the NT group (Table 4.4). If anywhere, the most consistent difference was found in V1, which is not an area in which a difference would be expected a priori.

Table 4.4. Results of univariate fMRI analysis

	Mean beta value across voxels		Difference between groups		
	ASD	NT	t_{44}	$p_{unc.}$	p_{FDR}
Inferior Occipital	0.92	1.02	1.08	.2841	> .5
Posterior Fusiform	0.63	0.73	1.37	.1762	> .5
Superior Temporal	0.34	0.37	0.40	> .5	> .5
Amygdala	0.30	0.27	0.46	> .5	> .5
Anterior Temporal	0.25	0.25	0.05	> .5	> .5
Inferior Frontal	0.30	0.32	0.35	> .5	> .5
V1	0.67	0.99	2.94	.0052	0.0937

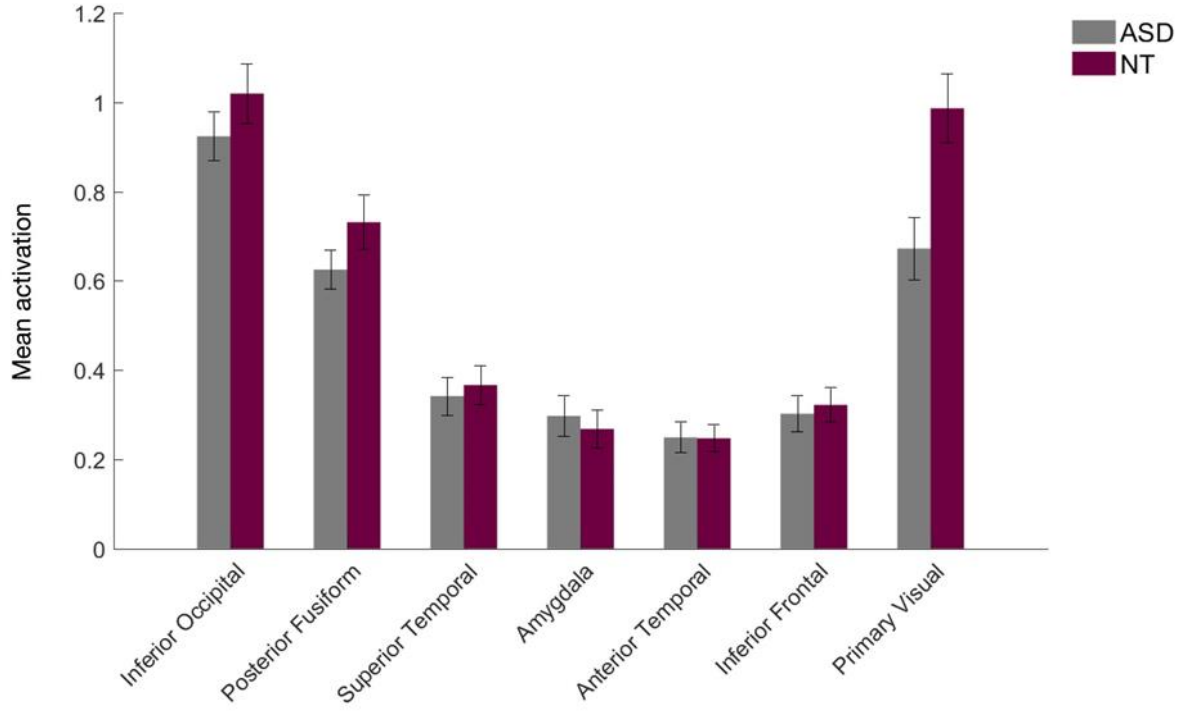

Figure 4.4. Results of univariate analysis. Average activation (mean beta-values) across all voxels within each of the ROIs for the "all faces versus fixation" contrast in both groups. No significant differences were found. Error bars display standard errors of the mean (SEM).

3.3. Multivariate fMRI results: decoding facial identity and expression

We performed ROI-based multi-voxel pattern analyses to investigate the quality of neural representations. In other words, we studied whether different facial emotions and identities can be decoded based on the neural activation pattern in a particular ROI. In addition, we tested for group differences in the quality of these neural representations. All statistical details are given in Table 4.5.

Firstly, different facial identities could be reliably distinguished based on neural responses in the inferior occipital cortex, the posterior fusiform cortex, and V1 in both groups. In addition, facial identity could be decoded from neural activation patterns in the inferior frontal cortex in the NT group, but not the ASD group (Figure 4.5A). Identities could not be reliably decoded from neural responses in the superior temporal cortex, the amygdala, and the anterior temporal cortex. Secondly, different facial expressions could be decoded from neural activation patterns in the inferior occipital cortex, the posterior fusiform cortex, the superior temporal cortex, and V1 in both groups (Figure 4.5B). Emotion could not be reliably distinguished based on neural responses in the other ROIs: the amygdala, the

anterior temporal cortex, and the inferior frontal cortex. Regarding the difference between the groups, we found no significant group differences in neural response patterns, in neither identity nor emotion.

Table 4.5. Results of multivariate analysis

		ASD			NT			Difference		
		t_{21}	$p_{unc.}$	p_{FDR}	t_{23}	$p_{unc.}$	p_{FDR}	t_{44}	$p_{unc.}$	p_{FDR}
Inferior Occipital	Identity	8.01	**<.0001**	**<.0001**	9.11	**<.0001**	**<.0001**	0.02	> .5	> .5
	Emotion	7.20	**<.0001**	**<.0001**	8.99	**<.0001**	**<.0001**	0.36	> .5	> .5
Posterior Fusiform	Identity	4.92	**.0001**	**.0004**	5.99	**<.0001**	**<.0001**	0.95	.3453	> .5
	Emotion	3.72	**.0013**	**.0077**	5.23	**<.0001**	**.0002**	0.57	> .5	> .5
Superior Temporal	Identity	2.64	**.0153**	.0696	1.38	.1822	> .5	1.02	.3133	> .5
	Emotion	3.25	**.0039**	**.0176**	4.05	**.0005**	**.0023**	0.18	> .5	> .5
Amygdala	Identity	0.74	.4654	1.4077	-0.71	.4869	> .5	0.15	> .5	> .5
	Emotion	0.18	> .5	> .5	1.68	.1065	.3220	0.97	> .5	> .5
Anterior Temporal	Identity	0.46	> .5	> .5	0.04	.9696	> .5	0.29	> .5	> .5
	Emotion	1.56	.1328	.4018	1.19	.2465	> .5	1.97	.0555	> .5
Inferior Frontal	Identity	1.95	.0643	.2334	2.87	**.0086**	**.0390**	0.23	> .5	> .5
	Emotion	2.53	**.0195**	.0707	1.84	.0787	.2856	0.30	> .5	> .5
V1	Identity	5.99	**<.0001**	**<.0001**	5.36	**<.0001**	**.0001**	0.28	> .5	> .5
	Emotion	6.50	**<.0001**	**<.0001**	5.05	**<.0001**	**.0002**	0.29	> .5	> .5

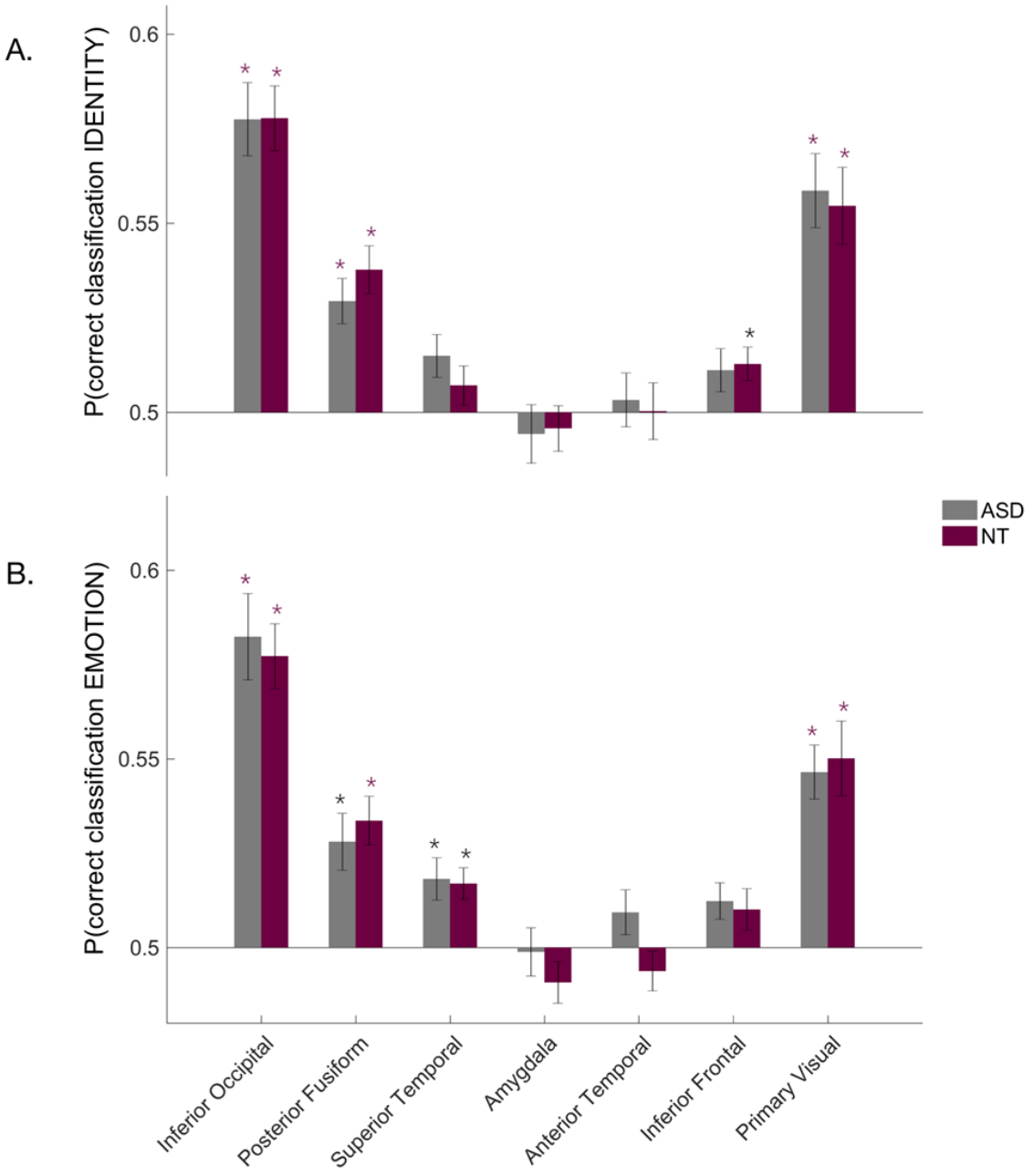

Figure 4.5. Results of multivariate analysis. (A) MVPA results for decoding of facial identity, FDR corrected. (B) MVPA results for decoding of facial emotional expression, FDR corrected. Red stars indicate a significance level of $p_{FDR} < .001$, while grey stars indicate a significance level of $.001 < p_{FDR} < .05$. Error bars display standard errors of the mean (SEM).

Finally, we wanted to check if particular regions of interest play a different role in identity versus emotion discrimination. For this purpose, we performed a repeated measures ANOVA with 'Decoding accuracy' as the dependent variable, 'Group' as between-subject factor, and within-subject factors 'Condition' (identity, emotion) and 'ROI' (restricted to the

ROIs that showed significant classification for both emotion and identity: inferior occipital cortex, posterior fusiform cortex, and superior temporal cortex). We found no significant interaction between ROI and Condition on decoding accuracy ($F_{2,225}$ = 0.69, p = .5008), suggesting that the ROIs play a similar role in the decoding of identity and emotion.

3.4. Adaptation fMRI results

We were interested in the differences in adaptation to faces between individuals with and without ASD. For this purpose, we calculated three adaptation indices by subtracting the 'AllSame' baseline from the three other conditions of interest (AllDiff, DiffId, DiffEmo). This resulted in three indices: 'AllDiff-AllSame', 'DiffId-AllSame', and 'DiffEmo-AllSame'. These adaptation indices captured the release from adaptation and were computed in both groups within each ROI. All statistical details are given in Table 4.6. Importantly, there were no significant differences between the groups concerning the average level of activation in the AllSame baseline condition ($t_{44} < 1.86$, $p_{unc.} > 0.0697$, $p_{FDR} > 0.50$, Figure 4.6A).

The first adaptation index ('AllDiff-AllSame') was significant in all ROIs in both groups. Hence, we observed a release from adaptation when a stimulus changed regarding both identity and emotion. Additionally, we found no group differences regarding the release from adaptation to identity and emotion simultaneously (Figure 4.6B).

The second adaptation index ('DiffId-AllSame') was significant in the inferior occipital cortex, the posterior fusiform cortex, the superior temporal cortex, the anterior temporal cortex, the inferior frontal cortex and V1. In the amygdala, the adaptation index was significant in neither of the groups. Hence, we observed a release from adaptation when a different facial identity was presented while the emotional expression remained stable in all ROIs except the amygdala. Additionally, we found no significant differences between the groups regarding the release from adaptation to identity (Figure 4.6C).

The third adaptation index ('DiffEmo-AllSame') was significant in the inferior occipital cortex, the posterior fusiform cortex, the superior temporal cortex, the inferior frontal cortex and V1. In both the amygdala and the anterior temporal cortex, we observed a non-significant adaptation index for the NT group, whereas it was significant in the ASD group. Thus, we observed a release from adaptation when a different facial expression was presented while the identity remained stable, in most ROIs. Additionally, we found no significant differences between the adaptation indices of both groups (Figure 4.6D).

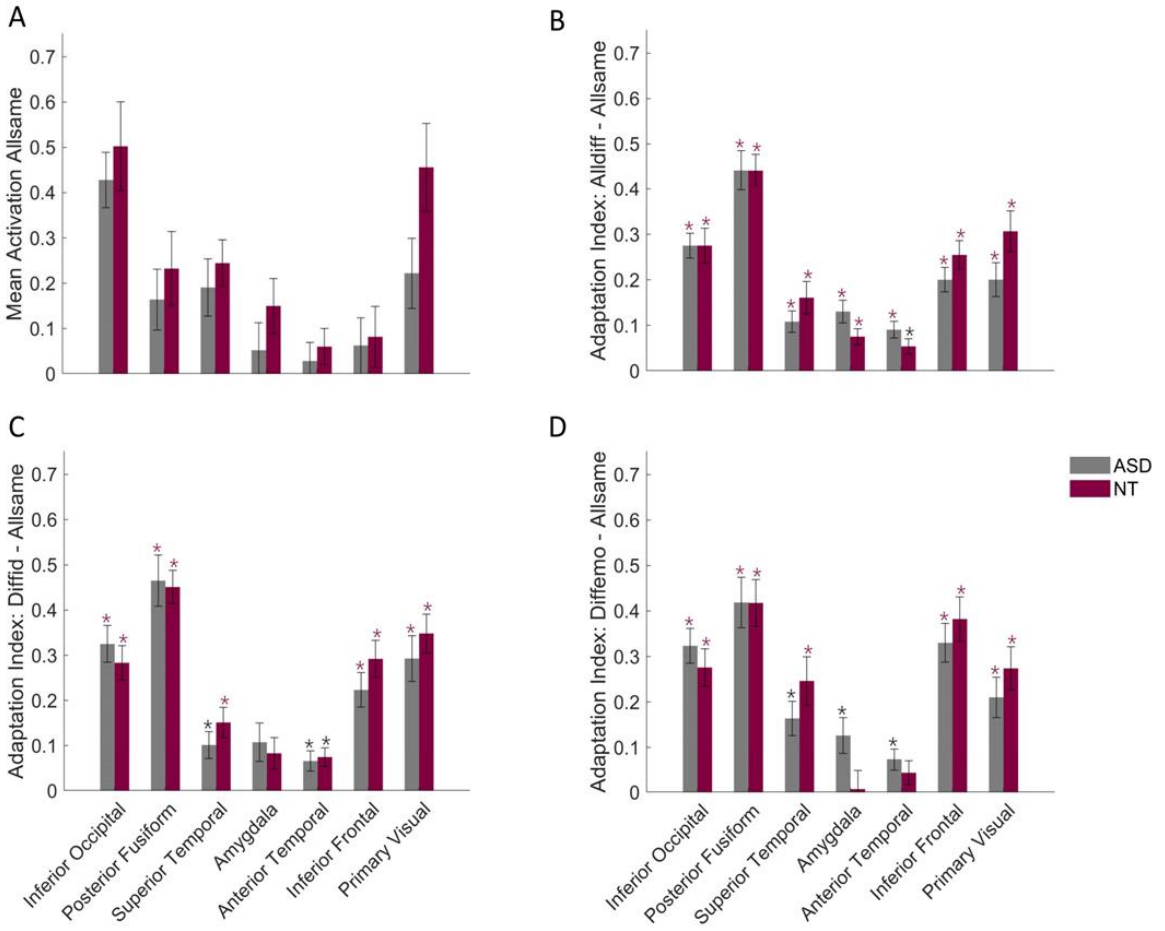

Figure 4.6. Results of adaptation analysis. (A) Average level of activation (beta-values) in the baseline condition ('AllSame'). (B) Results showing release from adaptation to changes in both facial identity and emotion (AllDiff-AllSame). (C) Results showing release from adaptation to changes in facial identity (DiffId-AllSame). (D) Results showing release from adaptation to changes in facial expression (DiffEmo-AllSame). Red stars indicate a significance level of $p_{FDR} < .001$, while grey stars indicate a significance level of $.001 < p_{FDR} < .05$. Error bars display standard errors of the mean (SEM).

Table 4.6. Results of adaptation analysis.

		ASD			NT			Difference		
	AI	t_{21}	p_{unc}	p_{FDR}	t_{23}	p_{unc}	p_{FDR}	t_{44}	p_{unc}	p_{FDR}
Inferior Occipital	AI_1	10.01	**<.0001**	**<.0001**	7.24	**<.0001**	**<.0001**	<0.01	> .5	> .5
	AI_2	7.98	**<.0001**	**<.0001**	7.44	**<.0001**	**<.0001**	0.75	.4575	> .5
	AI_3	8.49	**<.0001**	**<.0001**	6.75	**<.0001**	**<.0001**	0.85	.4003	> .5
Posterior Fusiform	AI_1	10.13	**<.0001**	**<.0001**	12.38	**<.0001**	**<.0001**	0.01	> .5	> .5
	AI_2	8.23	**<.0001**	**<.0001**	12.31	**<.0001**	**<.0001**	0.21	> .5	> .5
	AI_3	7.51	**<.0001**	**<.0001**	8.13	**<.0001**	**<.0001**	0.01	> .5	> .5
Superior Temporal	AI_1	4.64	**.0001**	**.0004**	4.51	**.0002**	**.0006**	1.21	.2336	> .5
	AI_2	3.43	**.0025**	**.0092**	4.54	**.0002**	**.0005**	1.10	.2733	> .5
	AI_3	4.30	**.0003**	**.0011**	4.63	**.0001**	**.0004**	1.24	.2220	> .5
Amygdala	AI_1	5.18	**<.0001**	**.0001**	4.25	**.0003**	**.0009**	1.81	.0771	> .5
	AI_2	2.52	**.0199**	.0516	2.40	**.0250**	.0649	0.45	> .5	> .5
	AI_3	3.24	**.0039**	**.0119**	0.17	.8633	2.2383	2.10	**.0419**	> .5
Anterior Temporal	AI_1	4.92	**<.0001**	**.0002**	3.25	**.0035**	**.0091**	1.48	.1471	> .5
	AI_2	2.96	**.0075**	**.0225**	3.62	**.0014**	**.0043**	0.29	> .5	> .5
	AI_3	3.07	**.0058**	**.0152**	1.62	.1181	.3573	0.83	.4132	> .5
Inferior Frontal	AI_1	7.47	**<.0001**	**<.0001**	8.03	**<.0001**	**<.0001**	1.30	.2010	> .5
	AI_2	5.87	**<.0001**	**<.0001**	7.15	**<.0001**	**<.0001**	1.22	.2282	> .5
	AI_3	7.74	**<.0001**	**<.0001**	7.93	**<.0001**	**<.0001**	0.81	.4245	> .5
V1	AI_1	5.42	**<.0001**	**.0001**	6.87	**<.0001**	**<.0001**	1.81	.0768	> .5
	AI_2	5.80	**<.0001**	**<.0001**	8.08	**<.0001**	**<.0001**	0.84	.4043	> .5
	AI_3	7.74	**.0001**	**.0005**	5.78	**<.0001**	**<.0001**	0.98	.3348	> .5

Note. AI_1: 'AllDiff-AllSame', AI_2: 'DiffId-AllSame', and AI_3: 'DiffEmo-AllSame'.

3.5. Functional connectivity

We investigated the functional connectivity among all pairs of ROIs, as well as potential group differences in connectivity. Within each group, we found that all pairwise connections between the investigated ROIs were significant with a critical p_{FDR} of 0.001 (ASD group: all $t_{21} > 3.67$, $p_{FDR} < 0.001$, Figure 4.7A; NT group: all $t_{23} > 3.50$, $p_{FDR} < 0.001$, Figure 4.7B).

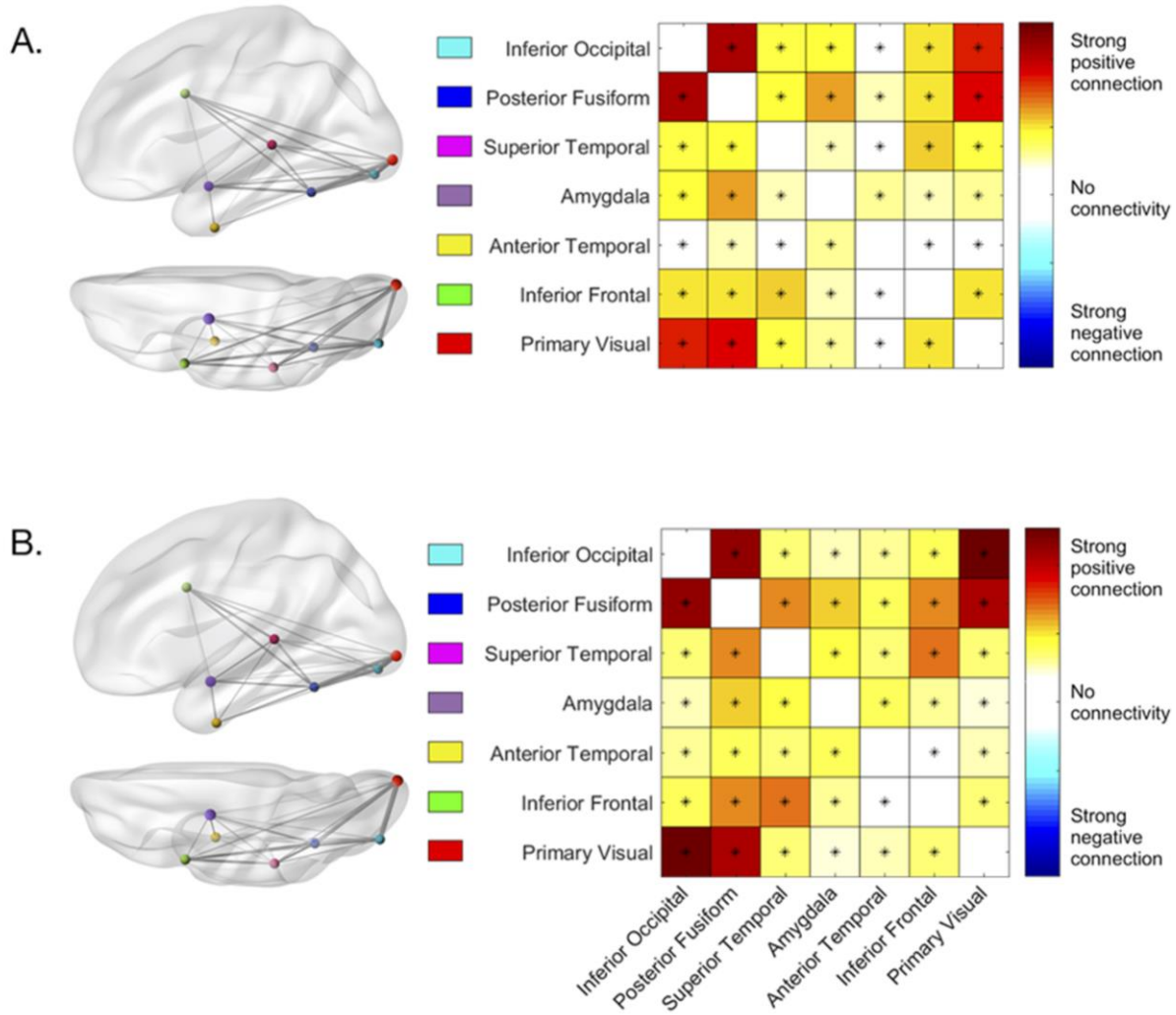

Figure 4.7. Functional connectivity levels in the ASD group (A) and in the NT group (B). Higher t-values (red) indicate a higher level of connectivity. Stars indicate pairs of regions that are significantly connected ($p_{FDR} < .001$). Within the brain, the thickness of the line indicates the strength of connection.

Next, we compared the patterns of connectivity between the ASD and NT groups (Figure 4.8). After FDR correction, we found significantly stronger connections in the ASD group between the amygdala and the inferior occipital cortex (t_{44} = 2.30, p_{FDR} = .0132), and the amygdala and V1 (t_{44} = 2.23, p_{FDR} = .0156).

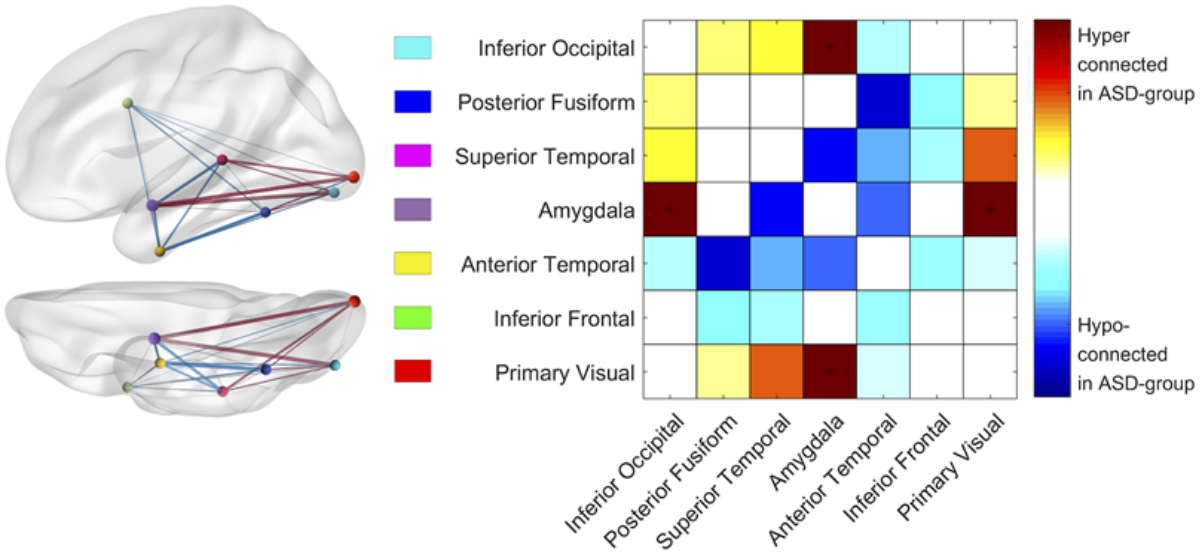

Figure 4.8. Differences in functional connectivity levels between the groups. Higher t-values (red) indicate higher connections in the ASD group, while lower values (blue) indicate weaker connections in the ASD group. Stars indicate significant differences between the groups at pFDR < .05. Within the brain, the thickness of the lines indicates the size of the group difference, with red lines signalling hyperconnectivity and blue lines signalling hypoconnectivity in the ASD group.

We checked whether individual differences in the number of acquired fMRI runs affected the observed group differences by running an ANCOVA on the functional connectivity data in every ROI-combination that showed a significant difference between the groups (i.e., inferior occipital cortex – amygdala and amygdala – V1). In our model, we included 'Connectivity' as a dependent variable, 'Group' as a between-subject factor and 'Number of runs' as a covariate. This additional ANCOVA revealed that group differences remained significant even when adding the number of acquired runs as a covariate: main effect of group on functional connectivity between the amygdala and the inferior occipital ($F_{1,43}$ = 5.19, p = .0277) and between the amygdala and V1 ($F_{1,43}$ = 5.01, p = .0304).

4. Discussion

4.1. Similar behavioural performance in ASD and NT

At the behavioural level, we did not find any differences between individuals with and without ASD concerning the recognition of facial identity and expression. Note that detailed inspection of the behavioural data shows that there is not even the slightest tendency for even a subthreshold group difference. Nevertheless, we intentionally selected tasks that should yield the highest chance of revealing group differences, as the face processing tasks did not allow mere perceptual matching (cf. Weigelt et al., 2012). Likewise, respecting the behavioural task in the scanner, we did not observe differences between groups, similar to Kleinhans and colleagues (2009). While behavioural studies have often demonstrated atypical facial identity (Tang et al., 2015; Weigelt et al., 2012) and facial expression processing (Harms et al., 2010; Uljarevic & Hamilton, 2013), this is certainly not a consistent finding (e.g., Adolphs et al., 2001; Kleinhans et al., 2009; Sterling et al., 2008). However, when studies do not show differences between the groups on standardised tests, this is typically in the case of children and adolescents (e.g., McPartland et al., 2011; O'Hearn et al., 2010) or familiar faces (e.g., Barton et al., 2004). Hence, although our finding seems quite unique for the studied population, it is not necessarily at odds with the more general literature. It is relevant to emphasise that we studied a sample of high functioning individuals. As far as they experience difficulties with face processing, they might have learned to compensate for these difficulties (Harms et al., 2010).

Note that the question about differences between groups at the neural level is not necessarily contingent upon general performance differences at the behavioural level. Studies often report similar behavioural performance (e.g., Pierce, 2001), which can be reached by different neural information processes. Furthermore, any observed neural difference would represent a genuine neural difference between the groups, as it cannot be a by-product of a behavioural inequality. In this regard, a recent series of EEG studies in school-aged boys with ASD versus matched controls showed highly significant group differences in neural processing of facial identity and expression. Neural differences were observed, even though the ASD participants were unimpaired on a large battery of

behavioural facial identity and expression processing tasks (Van der Donck et al., 2019, 2020; Vettori, Jacques, et al., 2019).

4.2. Similar univariate brain activity in ASD and NT

We found no significant differences in the average level of brain activity in response to dynamic face stimuli between individuals with and without ASD, in any of the ROIs. This is in line with several neuroimaging studies reporting equal face-evoked activity across groups (e.g., Aoki et al., 2015; Bird et al., 2006; Hadjikhani, Chabris, et al., 2004; Hadjikhani, Joseph, et al., 2004; Kleinhans et al., 2008). However, the bulk of previous studies did find group differences. These studies mainly reported hypoactivation of the fusiform gyrus, the superior temporal cortex, the amygdala, and the inferior frontal cortex in individuals with ASD. A few studies reported hyperactivation in the superior temporal cortex, the amygdala, and the anterior temporal cortex (for reviews and meta-analyses, see Aoki et al., 2015; Di Martino et al., 2009; Dichter, 2012; Nomi & Uddin, 2015; Philip et al., 2012).

It is not clear why we did not observe group differences, whereas other researchers did. A possible argument could be our fairly rough ROI definition at a normative anatomical level. Indeed, Kleinhans and colleagues (2008) defined their fusiform region in a similar anatomical way, and they did not observe any group differences in activation either. However, even when a strictly defined subject-specific fusiform face area is used, a difference in activity between individuals with and without ASD is not consistently reported (e.g., Hadjikhani, Joseph, et al., 2004). Another explanation for our inconsistent findings may be the contrast we used to calculate univariate activity. Here, we contrasted neural activity when participants were looking at dynamic faces with neural activity when looking at a fixation cross. Most previous studies have used more specific contrasts, such as faces versus objects (e.g., Humphreys et al., 2008) or emotional faces versus neutral faces (e.g., Critchley et al., 2000). However, Pelphrey et al., (2007) applied an identical contrast, comparing brain activity during dynamic face processing versus presentation of a fixation cross. Contrasting our results, they did observe differences between adults with and without ASD in several face-sensitive regions, including hypo-activation in the fusiform gyrus and the amygdala. Finally, a major difference between our study and most other studies is that ours was tailored towards the detection of subtle differences in the quality of facial representations via MVPA and adaptation fMRI analysis, and therefore entailed many more trials and runs than conventional subtraction-based fMRI studies. As a result, it is

plausible that minor group differences in activity level of the face processing network may have been eliminated, because both participant groups reached maximal plateau level due to the repeated stimulation. Although speculative, supporting evidence for this reasoning is found in the observation that other studies pinpointing social cognition in ASD via extensive MVPA fMRI designs did not observe group differences in basic activity level even though they did observe group differences in the neural representations (e.g., Lee Masson et al., 2019).

Unexpectedly, we did observe a significant (uncorrected) group difference in activity level in V1, even though it did not survive FDR correction. This finding contrasts with findings of Hadjikhani and colleagues (Hadjikhani, Chabris, et al., 2004) who reported normal activity levels in early visual areas in ASD during face processing. Moreover, the direction of the group difference in V1 (increased activity in NT compared to ASD) contrasts with findings of the general perceptual neuroimaging literature of ASD. Indeed, generally, if group differences in brain activity are observed, individuals with ASD typically show reduced activity in higher-level social brain areas and increased activity in low-level primary visuo-perceptual areas (Samson et al., 2012). This particular pattern has been interpreted as evidence for impaired holistic and predictive processing, and increased mobilisation of low-level perceptual strategies in ASD (Mottron et al., 2006; Sapey-Triomphe et al., 2020; Van de Cruys et al., 2014).

4.3. Similar neural representations in ASD and NT

We were able to consistently classify different emotions and identities based on neural activity patterns in a series of face-responsive brain regions. We observed this was possible in the inferior occipital cortex, the posterior fusiform cortex, and V1 for both identity and emotion, and in the superior temporal cortex for emotion but not identity. Generally, we did not observe any robust anatomical specificity for the sensitivity in decoding of identity versus emotion.

Our results are largely consistent with previous fMRI studies showing significant decoding based on neural responses of face identity in the inferior occipital cortex, the fusiform gyrus and V1 (Anzellotti et al., 2014; Goesaert & Op de Beeck, 2013; Nestor et al., 2011, 2016; Nichols et al., 2010); and of facial expression in the inferior occipital cortex, the fusiform gyrus, the superior temporal cortex and V1 (Harry et al., 2013; Wegrzyn et al., 2015). Furthermore, the levels of decoding in our study are comparable to decoding levels in

previous studies, but the p-values are lower, probably because we have a larger number of participants. In contrast to previous fMRI studies, we did not find significant identity decoding based on neural responses in the anterior temporal cortex (Anzellotti et al., 2014; Goesaert & Op de Beeck, 2013; Kriegeskorte et al., 2007), the superior temporal cortex or the inferior frontal cortex (Nestor et al., 2016). Also contrasting some findings in the literature, we did not find significant decoding of facial expressions based on neural responses in the anterior temporal cortex and the amygdala (Wegrzyn et al., 2015).

Most importantly in the present context, we tested whether the two groups differed in terms of the quality of neural representations. Thus far, as far as we know, only one MVPA study investigated potential differences in facial (expression) representations in ASD. This study yielded evidence for intact facial expression representations in adults with ASD (Kliemann et al., 2018). Likewise, we found no convincing evidence for differences in the quality of neural facial representations, not in terms of identity nor in terms of expression processing. The anterior temporal ROI was the only region where a trend was present, showing a slightly increased decoding of facial expression based on neural responses in ASD (two-tailed uncorrected $p = 0.0555$). It could be argued that we should be careful before excluding the possibility that there might be a small effect in that region. Nevertheless, we had no a priori hypothesis that there would be an effect confined to the anterior temporal cortex, and the group difference resulted from the combination of non-significant above-chance decoding in ASD and non-significant below chance decoding in NT. Furthermore, we observed an effect in the opposite direction than what would be expected given the literature about lower facial emotion recognition performance in ASD. For these reasons we think it is appropriate to only look at the p-values corrected for multiple comparisons. Hence, we found no indication for any group difference in quality of facial identity and expression representations in any of the ROIs.

4.4. Similar adaptation to identity and expression in ASD and NT

We found significant activity in our baseline (AllSame) condition within all ROIs and significant adaptation indices in almost all ROIs (except the anterior temporal cortex and the amygdala). This indicates a significant release from adaptation in almost all ROIs when a change in identity, emotion or both occurs. Our findings are in line with the finding of adaptation to repeated identity in the inferior occipital cortex, the fusiform gyrus, and the superior temporal cortex (Andrews & Ewbank, 2004; Winston et al., 2004; Xu & Biederman,

2010), and adaptation to repeated expression in the fusiform gyrus (Xu & Biederman, 2010) and the STS (Winston et al., 2004). However, our findings partly contrast the findings of Andrews and Ewbank (2004), who did not find adaptation to repeated identities in the superior temporal lobe.

Furthermore, we did not find significant differences in adaptation to faces between ASD and NT participants. These findings contrast with results obtained by Ewbank and colleagues (2017), who found reduced adaptation to neutral faces in individuals with ASD. In addition, this contradicts the finding of reduced neural habituation in the amygdala in ASD individuals (Swartz et al., 2013). The difference between our results and previous findings could be due to differences in the studied population, as Swartz and colleagues (2013) studied children and adolescents. Another way to account for the difference could be the task, as we used a task in which participants focused on the emotion and identity of faces, while the two aforementioned studies used an implicit task.

4.5. Slight functional connectivity differences in face processing

We studied intrinsic functional connectivity between all seven ROIs by regressing out the task-based activity. In addition, we assessed possible differences between individuals with and without ASD. We opted to investigate this artificial resting-state functional connectivity, because a targeted task-based functional connectivity analysis was not compatible with the design of this study. In particular, task-based functional connectivity entails a contrast between tasks or stimuli, which was not possible due to the combined presentation of both conditions (identity and emotion) at the same timepoint.

We found that all ROIs implicated in the extended face processing network show a pattern of temporal co-activation. Thus, all regions seem to be working closely together when processing dynamic faces in both groups. This is in line with the literature that has identified these ROIs as being relevant for face processing and previous studies showing significant connections between these regions in both groups (Kleinhans et al., 2008). Whereas we observed a pattern of significant temporal co-activation between all ROIs, there was still some differentiation in the pattern of functional connections. Some areas, such as the inferior occipital cortex, the posterior fusiform cortex and V1 were very strongly co-activated in both groups. In contrast, the amygdala and the anterior temporal cortex showed an overall relatively weaker functional connectivity with other regions.

When comparing individuals with and without ASD regarding intrinsic functional connectivity of the face processing network, we noticed atypical functional connectivity patterns for the amygdala. In particular, the ASD group showed stronger functional connections between the amygdala and lower-level visual areas (i.e., V1 and the inferior occipital cortex). This specific finding has not been observed in previous studies. Earlier studies, using various task paradigms, have suggested atypical functional connectivity, mainly involving hypoconnectivity among several face-sensitive regions in the ASD group, but results are not consistent. For instance, Wicker and colleagues (2008) adopted an effective functional connectivity approach using dynamic facial expression stimuli. They demonstrated that occipital cortex activity had a weaker influence on activity in the fusiform gyrus in adults with ASD. Kleinhans et al. (2008) applied a task-based functional connectivity analysis contrasting faces and houses to reveal reduced connectivity between the fusiform gyrus and the amygdala in the ASD group. Koshino and colleagues (2008) also used a task-based approach contrasting faces and fixation and found reduced connectivity between the fusiform gyrus and the inferior frontal cortex in individuals with ASD. Finally, studies comparing individuals with and without ASD on resting-state fMRI data also typically observed hypoconnectivity among several face-related regions, including the fusiform gyrus, the superior temporal sulcus, and the amygdala (e.g., Abrams et al., 2013; Alaerts et al., 2013; Anderson et al., 2011; Guo et al., 2016). For an overview of pooled resting-state fMRI studies in ASD, see the ABIDE consortium web pages (http://fcon_1000.projects.nitrc.org/indi/abide/; Di Martino et al., 2014; Di Martino et al., 2017) and recent reviews (Hull et al., 2017; Lau et al., 2019).

Note that hypoconnectivity has not been unanimously observed either, and that some authors observed functional hyperconnectivity in occipitotemporal brain regions (e.g., Keown et al., 2013; Supekar et al., 2013). Others have emphasised the individual variability and idiosyncrasy of spontaneous connectivity patterns in the autistic brain (Hahamy et al., 2015). In this regard, our observation of functional hyperconnectivity between the amygdala and the inferior occipital cortex, and the amygdala and V1 in the ASD group may be relatively uncommon but not irreconcilable with previous research. Rather, it adds yet another way functional connectivity -especially of the face processing network- can be atypical in individuals with ASD. We can attribute the inconsistency of results to the use of various designs and analysis approaches and/or to the heterogeneity of individuals on the autism spectrum. Our findings suggest that the amygdala functions differently in the face processing network in the ASD group, while overall each node is still equally activated. Speculatively, as the amygdala is involved in attributing salience and emotional valence to

perceptual input (Adolphs, 2010), the stronger functional connectivity between the amygdala and two low-level visual regions may suggest that individuals with ASD attribute emotional meaning to more basic perceptual features of the face, instead of emphasising the higher-level integrative socio-communicative cues.

4.6. Methodological considerations

In our study, we used dynamic stimuli to investigate the processing of facial identity and expression, while previous studies have mostly used static stimuli. Dynamic stimuli are suggested to be more ecologically valid, therefore possibly enabling to reveal the atypical activation and connectivity patterns more robustly in individuals with ASD (Law Smith et al., 2010; Sato et al., 2012). Indeed, it has been shown in typical participants that dynamic facial stimuli yield stronger activations in social brain regions (the fusiform gyrus, the superior temporal cortex, the inferior frontal cortex, and the amygdala) compared to static facial stimuli (Kilts et al., 2003; LaBar et al., 2003; Sato et al., 2004; Schultz & Pilz, 2009; Trautmann et al., 2009). Individuals with ASD seem to be lacking this enhanced response to dynamic stimuli, shown in studies directly comparing responses to dynamic and static facial stimuli in individuals with ASD and neurotypicals (Pelphrey et al., 2007; Sato et al., 2012). In response to dynamic facial stimuli, individuals with ASD showed hypo-activation in the fusiform gyrus (Pelphrey et al., 2007), the superior temporal cortex (Wicker et al., 2008), and the amygdala (Pelphrey et al., 2007). When looking at visual movement in general, decreased responses in V1 have been observed in individuals with ASD compared to neurotypicals (Robertson et al., 2014). Hence, dynamic (facial) stimuli seem to yield higher responses and larger differences between the groups. As we only observed subtle differences between the groups in terms of functional connectivity, our findings are not in line with the finding of enhanced responses to dynamic stimuli. However, our findings are in line with the only other MVPA study in this domain -that also used dynamic facial stimuli- observing no differences between the groups.

As mentioned before, our design was based on the continuous carry-over design of Aguirre (2007). This approach was proposed in a theoretical paper (Aguirre, 2007), and applied in several empirical papers (e.g., Drucker & Aguirre, 2009). Aguirre (2007) argues that this type of design can be used to measure 'direct effects': the mean response to a certain condition (e.g., mean response to sad faces). In addition, it can be used to measure 'carry-over effects': how a stimulus is influenced by a previous stimulus (adaptation effects,

e.g., 'AllSame' vs 'DiffEmo' trials). Similar to the original continuous carry-over design, our design had short trials presented in a continuous, sequential way. However, our design is not identical to the original continuous carry-over design. The main difference is that we worked with "short blocks of variable length" while Aguirre used an event-related approach. With our approach, we increased the likelihood that a condition followed itself, resulting in a much higher frequency of 'AllSame' trials (current trial same as previous trial). Without going into detail, we believe our approach has some benefits to the original approach both because it increases the power of the MVPA (as block designs are more sensitive given the low temporal resolution of fMRI), and because it makes repetitions more frequent and expected, increasing adaptation in the same trials (as shown by Summerfield et al., 2008).

4.7. Limitations

Our study has several limitations, which are important to mention. First, the participants in our ASD group were mainly high functioning adults. Our design required participants to spend a prolonged period inside the scanner without moving, and low functioning individuals tend to have difficulties with this. As a result, group differences may have been underestimated, and this refrains us from generalising conclusions to the larger ASD population (Nomi & Uddin, 2015; Simmons et al., 2009). Second, in line with the previous point, we found a significant group difference for the number of fMRI runs acquired for each participant. The number of runs was on average smaller in the ASD group as compared to the NT group. Note however that we included the number of runs as a covariate when relevant. Third, we were not able to acquire separate localiser scans for all our (ASD-)participants because the experimental situation was over-demanding. As a result, ROIs could not be independently defined based on subject-specific localiser scans. It is possible that more specific effects would have been demonstrated if ROIs were defined based on face selectivity at the individual level. Fourth, ADOS and ADI scores were not available for all ASD participants. Many of our participants were diagnosed before these instruments became routine, and they are not yet routinely administered within the clinical trajectory of adult populations at this time. As a result, we were unable to report ADOS and ADI scores. These scores would have been relevant to attain comparability to other studies and to quantitatively confirm ASD diagnoses. Finally, while our sample size was sufficient to find group differences with a large effect size, it was not appropriate to find very small effects. While we can conclude that no large differences appear to be present between

ASD and NT in many of our analyses, it is possible that we missed small effects showing large within-group variability. This is particularly relevant because large variability has been reported in ASD, even among high functioning individuals (e.g., Pegado et al., 2020).

4.8. Global discussion

The strength of the present study is the combination of five analysis methods tailored towards investigating five different hypotheses. These methods addressed the performance on facial identity and expression processing tasks (behavioural analyses), the general involvement of different processes (univariate analysis), the quality of neural representations involved (MVPA), the degree of repetition suppression (adaptation analysis), and the connectivity between the involved regions (functional connectivity analysis).

Contrary to our expectations and the bulk of literature, we found that individuals with ASD are very similar to neurotypicals with respect to the measures investigated in this study. The fact that our findings are not consistent with most of the literature, and the inconsistent nature of the literature as a whole, is likely due to the large variance in designs and approaches across studies, as well as the considerable heterogeneity of the ASD population. The lack of significant differences between the groups suggests that individuals with ASD perceive and categorise facial identity and expression similar to neurotypicals. We only observed that the amygdala in individuals with ASD is hyperconnected to low-level brain areas in the face processing network. Although not reported in the general ASD literature, this pattern may suggest that individuals with ASD attribute meaning to more basic perceptual features of the faces, as the amygdala is involved in attributing salience and emotional valence to the perceptual input (Adolphs, 2010). This may resonate with basic physiological findings showing that faces are experienced as more arousing by individuals in ASD (Tanaka & Sung, 2016), and therefore possibly also as more aversive (Robinson, 2007). However, our study suggests that this initial over-reactivity does not seem to affect the further higher-level behavioural and neural processing of faces in terms of identity or expression.

We investigated the neural representation of faces and the neural adaptation to faces in terms of identity and expression separately. This choice was made based on both the dominant face perception framework proposed by Haxby and colleagues (Haxby, Hoffman, et al., 2000), with its separate pathways for variant and invariant facial features; and the

dominant view of Bruce and Young (Bruce & Young, 1986), in which identity and expression are two parallel - and thus independent - neural routes. Arguments in favour of this two-pathway framework are extensive and beyond the scope of this paper. Applied to the current study, we would have expected to find a difference in decoding accuracies and release from adaptation between identity and emotion in different regions of interest. More specifically, to support this framework, decoding of and adaptation to facial identity would respectively be expected to yield higher decoding accuracies and stronger release from adaptation in identity-related brain regions, such as the fusiform gyrus and the anterior temporal cortex. Contrarily, decoding of and adaptation to facial emotion would respectively be expected to yield higher decoding accuracies and stronger release from adaptation in expression-related brain areas, such as the superior temporal cortex and the amygdala. Evidently, this is not what we found, as representations of identity and emotion in the studied brain areas were very similar and the observed release from adaptation to identity and emotion was very alike. Correspondingly - notwithstanding the popularity of the dominant framework - researchers have argued that the processing of facial identity and expression is, at least somewhat, related (Calder & Young, 2005; Xu & Biederman, 2010; Yankouskaya et al., 2017). In line with this argument, it has been shown that brain areas involved in the processing of identity also respond to facial expressions (LaBar et al., 2003; Schultz & Pilz, 2009; Winston et al., 2004). Similarly, brain areas involved in facial expression processing are also activated while processing facial identity (e.g., Dobs et al., 2018; Fox et al., 2011). The findings of our multi-voxel pattern analysis and adaptation analysis also support this more recent argument that recognition of facial identity and expression are in fact related. Altogether, the relation between facial identity processing and facial expression processing seems to be very similar in individuals with ASD and neurotypicals.

In this study, we found differences in functional connectivity in the absence of differences in behavioural performance, overall activity, or neural representations. We have encountered a similar situation before in the context of another neurodevelopmental disorder, dyslexia. In that case, speech processing regions contained equally robust representations in individuals with dyslexia as in typical readers, but some regions were hypoconnected in the dyslexia group (Boets et al., 2013). Together, such findings provide evidence in favour of an atypical access theory of the implicated neurodevelopmental disorder, without any differences at the representational level. Based on our findings, it seems that the amygdala is connected differently (i.e., more strongly connected to lower-level areas) in individuals with ASD.

4.9. General conclusion

To summarise, we observed no differences between high functioning adults with ASD and age- and IQ-matched neurotypicals regarding behavioural face processing performance, neural activity levels while processing faces, quality of neural representations of facial identity and expressions, and release from adaptation among the face processing network. In terms of disparities, we only observe subtle differences in how the amygdala is connected to the inferior occipital cortex and V1: two low-level regions in the face processing network. However, as face processing in daily life happens in the blink of an eye, these subtle connectivity differences could significantly impede the interpretation of complex facial signals and explain hardships individuals with ASD often endure in real life social situations.

Chapter 5

Understanding face processing in ASD using frequency-tagging EEG

Abstract

The fluent processing of faces is vital for successful social interactions. Yet, individuals with autism spectrum disorder (ASD) can experience difficulties with the processing of both facial identities and expressions. The goal of this study was to compare the neural sensitivity to changes in facial identity and expression between adults with and without autism spectrum disorders.

Behavioural and electroencephalography (EEG) data were acquired from 37 men, 18 with a formal ASD diagnosis and 19 age- and IQ-matched neurotypical controls. We applied fast periodic visual stimulation (FPVS) and used frequency-tagging EEG to assess the neural sensitivity to implicitly detect subtle changes in facial identities and facial expressions. In both paradigms, a stream of 'base stimuli' was presented at 6 Hz, periodically interleaved with an 'oddball stimulus' every fifth stimulus (1.2 Hz oddball rate). In the facial identity paradigm, faces of one identity were presented as base stimuli, interleaved with oddball stimuli of faces belonging to different identities. In the facial expression paradigm, a stream of neutral 'base' faces was presented, interleaved with expressive 'oddball' faces (i.e., angry, fearful, happy, and sad; in separate sequences). The use of frequency tags (i.e., 6 Hz for base stimuli, 1.2 Hz for oddball stimuli) allowed quantification of the facial identity and expression discrimination responses in an objective manner. It is the first time this frequency-tagging EEG technique was used to study the processing of facial expressions in an adult ASD population.

We observed no differences between individuals with and without ASD on a behavioural facial expression processing task, nor in base or oddball EEG responses of either the facial identity or expression paradigm. Likewise, the face inversion effect was similarly present in both groups. Overall, our findings indicate that high functioning male adults with and without ASD have a similar neural sensitivity to changes in facial identities and facial expressions.

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1. Introduction

The success of social interactions has been suggested to rely heavily upon the ability to effectively process faces (Haxby et al., 2002). Luckily, most people can process faces extraordinarily well, both in terms of identity recognition and emotional expression processing (Tanaka, 2001). Nevertheless, individuals with autism spectrum disorder (ASD) might experience difficulties in both domains (Barton et al., 2004; Harms et al., 2010; Tang et al., 2015; Uljarevic & Hamilton, 2013; Weigelt et al., 2012). These difficulties may even underly the social hardship individuals with ASD can experience (Dawson et al., 2005; Nomi & Uddin, 2015; Schultz, 2005). In this study, we investigated facial identity and expression processing in adults with ASD and matched neurotypical (NT) controls using frequency-tagging electroencephalography (EEG) in combination with fast periodic visual stimulation (FPVS).

1.1. Behavioural face processing in ASD

Face processing has been studied abundantly, in ASD as well as typical populations. The experimental evidence for ASD-related atypicalities in behavioural indices of face processing is mixed.

Regarding facial identity processing, reviews have reached inconsistent conclusions. Individuals with ASD across age groups do not show impairments on simple perceptual face processing tasks, in which stimuli are presented simultaneously. However, tasks involving even a small memory component, higher task demands or involving expressions generally yield poorer performance in ASD (Weigelt et al., 2012). Systematic differences in response times have not been observed. Nevertheless, when higher response times are reported, studies often included adults with ASD (Tang et al., 2015; Weigelt et al., 2012). Similarly, differences between individuals with and without ASD of all age groups have been observed regarding standardised face recognition tasks. When similar performance on these tasks was observed, studies included children or adolescents (Weigelt et al., 2012). It is still debated whether individuals with and without ASD use the same strategy to process facial identities (Tang et al., 2015; Weigelt et al., 2012). In this regard, an important line of research has suggested that individuals with ASD may process faces less holistically,

as evidenced by a reduced face inversion effect (O'Brien et al., 2014; Vettori, Dzhelyova, et al., 2019), although this finding is not consistent (Hedley et al., 2015; Tavares et al., 2016).

The empirical evidence in terms of facial expression processing is mixed as well, in particular for studies involving basic emotions. Findings vary from reports of general ASD-related difficulties with the recognition of all emotions, to specific difficulties (e.g., for one specific emotion or only for negative emotions), to no differences between individuals with and without ASD (Harms et al., 2010; Uljarevic & Hamilton, 2013). Although the literature is inconsistent, group differences are most frequently reported for the processing of negative emotions, complex emotions, and in studies with higher task demands such as fast presentation rates or low intensities of presentation (Harms et al., 2010; Lozier et al., 2014; Uljarevic & Hamilton, 2013). In addition, research shows that differences in facial expression processing between individuals with and without ASD increase with age (Lozier et al., 2014). Accordingly, intact facial expression recognition in ASD has only been observed in children (Lacroix et al., 2014; Leung et al., 2013; Tracy et al., 2011).

1.2. Event-related potentials (ERP) face processing studies

In recent years, EEG has often been used as a tool to study face processing in the brain, frequently with classic approaches such as event-related potentials (ERPs) (Jeste & Nelson, 2009; Luckhardt et al., 2014). One particularly important ERP component for face processing is the N170 component (Hinojosa et al., 2015). It was even suggested that this component may act as a neural biomarker for ASD-related atypical social-communicative functioning (Kang et al., 2018). However, this suggestion has been debated, as atypicalities in this component are not necessarily autism specific (Feuerriegel et al., 2015) and can also be due to a slower processing of social stimuli in general (Vettori, Jacques, et al., 2019).

Electrophysiological studies about facial identity processing have reported inconsistent results, with reports of intact as well as atypical N170 latencies and amplitudes in children and adults with ASD (Hileman et al., 2011; McPartland, Wu, et al., 2011; Neuhaus et al., 2016). A recent meta-analysis found the N170 latency to faces to be slightly but significantly delayed in ASD (Kang et al., 2018). Studies in adult ASD populations are sparse, and the few conducted studies have yielded inconsistent results. Accordingly, intact N170 latencies and amplitudes have been observed in adults with ASD, in the absence of a behavioural face inversion effect (Webb et al., 2012). In contrast, atypical N170 latencies and amplitudes in ASD have also been observed, with an intact behavioural face inversion effect (Tavares et al., 2016).

Electrophysiological facial expression research has reported inconsistent results, with findings of intact but more often atypical P100 and N170 latencies and amplitudes (Batty et al., 2011; Black et al., 2017; Monteiro et al., 2017; Wong et al., 2008). Facial emotion processing research in adults with ASD using ERPs is scarce. A few studies in adult populations find delayed N170 latencies in ASD (O'Connor et al., 2005, 2007), and one also found smaller N170 amplitudes and delayed P100 latencies in ASD (O'Connor et al., 2005). Other studies report intact N170 and P100 amplitudes and latencies in adults with ASD (Faja et al., 2016; Magnée et al., 2011; 2008; Tseng et al., 2015).

1.3. Fast periodic visual stimulation frequency-tagging EEG

Although the classical ERP approach has often been used, it also presents some disadvantages. Recordings can often take a long time, as many trials are needed due to the low signal-to-noise ratio of this approach. Furthermore, subjective choices must be made throughout the analysis, such as the selection of time windows and determination of ERP components. Therefore, we applied an alternative approach to investigate face processing in adults with and without ASD, using a combination of fast periodic visual stimulation (FPVS) and frequency-tagging EEG. FPVS-EEG relies on the fact that the oscillation frequency of the brain synchronises with the periodicity of the visual stimulation (Adrian & Matthews, 1934; Norcia et al., 2015). Moreover, different categories of stimuli can be presented at distinct predefined frequencies, thereby allowing to pinpoint the neural sensitivity for each of these categories. More specifically, in our oddball paradigms, an "oddball stimulus" is presented periodically in a stream of "base stimuli". For instance, base stimuli can be presented at a predefined rate of 6 Hz, interleaved with an oddball stimulus every fifth image, thus at a predefined rate of 1.2 Hz. Because the stimuli are presented at distinct frequency rates, we can easily and objectively disentangle and quantify the EEG responses (Liu-Shuang et al., 2014). Importantly, a synchronised neural response at the 1.2 Hz oddball frequency tag appears in the frequency domain only if the brain automatically categorises the oddball stimulus as being different from the base stimuli.

This FPVS-EEG approach has many benefits (Rossion, 2014). Firstly, it allows for implicit measurements of the electrophysiological response. An explicit task is not needed, as neural synchronisation to periodic stimulation happens automatically. Secondly, it is an objective measurement since the response occurs at predefined frequencies. Thirdly, responses are easily quantified by contrasting the response of interest (i.e., response at the oddball frequency) with noise (i.e., response at adjacent frequencies). Fourthly, FPVS-EEG

is a robust technique with a high signal to noise ratio (SNR). It seems to be immune to artefacts, yielding highly reliable responses, even at the individual subject level. Finally, it is fast to acquire, providing powerful results in only a few minutes.

Recently, the FPVS-EEG approach was introduced in autism research to investigate potential group differences in automatic facial identity and expression discrimination in school-aged children with and without ASD (Van der Donck et al., 2019, 2020; Vettori, Dzhelyova, et al., 2019). Importantly, despite intact performance on a series of behavioural facial identity and expression processing tasks, these paradigms yielded highly significant group differences in neural processing. Researchers observed the facial identity processing of upright but not inverted faces to be atypical in children with ASD, indicating the absence of a neural face inversion effect in ASD (Vettori, Dzhelyova, et al., 2019). In addition, researchers observed an emotion-specific processing deficit in ASD: boys with ASD were less sensitive than neurotypical boys to implicitly detect angry and fearful faces, but not sad and happy faces (Van der Donck et al., 2020). Nonetheless, application of a very similar FPVS-EEG facial identity paradigm in adults with and without self-reported ASD did not reveal any group differences (Dwyer et al., 2019). Thus far, no study used this same FPVS-EEG approach to investigate facial expression processing in adults with and without ASD.

1.4. Current study

In the current study, we used an FPVS-EEG approach to study the neural sensitivity to changes in facial identities and expressions in adults with and without ASD. More specifically, we used paradigms previously established in children (Van der Donck et al., 2020; Vettori, Dzhelyova, et al., 2019). In line with previous findings in children, we expected reduced neural sensitivity to changes in facial identity and facial expression in adults with ASD. In addition, in line with studies indicating impaired holistic processing in individuals with ASD, we anticipated a reduced neural face inversion effect in the ASD group. Furthermore, we expected to observe neural atypicalities in facial expression processing similar to the robust findings in children. Although adults with ASD may have developed various perceptual and cognitive strategies to consciously compensate for underlying face processing deficits (Livingston et al., 2019), we hypothesised that the fast presentation rate of the FPVS approach would put the neural system under pressure, therefore allowing us to reveal reduced sensitivity for subtle changes in facial identity and expression, even in high functioning adults with ASD.

2. Methods

2.1. Participants

Thirty-seven men (N_{ASD} = 18, N_{NT} = 19) aged between 19 and 35 years old participated in this study. Participants completed informed consent prior to participation. The study was approved by the Medical Ethics committee of the University Hospital Leuven (UZ Leuven).

Individuals with ASD were recruited through the Leuven Autism Expertise Centre (ECA) and the University Psychiatric Centre KU Leuven (UPC Leuven). All participants with ASD were diagnosed by a multidisciplinary team. Four participants with ASD had comorbid attention deficit (hyperactivity) disorder. No other comorbid psychiatric conditions were reported. Two participants with ASD were lefthanded and one was ambidextrous. NT individuals were recruited through online advertising. None of the NT participants had a history of psychiatric conditions. One NT participant was ambidextrous. None of the participants took psychotropic medication or used oxytocin presently or in the past. All participants had normal or corrected-to-normal vision, and a total IQ above 70.

Table 5.1. Age and IQ-measures for both groups, and difference between groups

	ASD				NT				Difference	
	Mean	Min	Max	SD	Mean	Min	Max	SD	T	p
Age	26.11	19	35	5.59	25	19	34	4.31	0.68	0.5015
Verbal IQ	104.83	68	134	17.98	106.63	90	140	11.65	0.36	0.7188
Performance IQ	109.28	62	153	22.27	106.95	74	137	18.34	0.35	0.7297
Total IQ	107.22	73	147	21.29	107.58	88	141	15.35	0.06	0.9535

To ensure matching of the ASD and NT groups, we measured intelligence quotient (IQ) using four subtests of the Wechsler Adult Intelligence Scale (WAIS-IV-NL): block design, similarities, vocabulary, and visual puzzles. This allowed for the computation of verbal, performance, and total IQ. Groups were successfully matched in terms of age and total,

verbal, and performance IQ (Table 5.1). Participants in both groups showed an intelligence slightly above average.

2.1.1. Scales measuring autistic traits

To measure autistic traits, a Dutch version of the Social Responsiveness Scale for adults (Constantino & Todd, 2005; Noens et al., 2012) was administered. This scale measures autistic traits, with subscales 'social awareness', 'social communication', 'social motivation' and 'restricted interests and repetitive behaviour'. Reported scores are T-scores, with higher scores indicating the presence of more autistic traits. In addition, we administered a Dutch version of the Autism-spectrum Quotient (AQ) (Baron-Cohen et al., 2001; Hoekstra et al., 2008). Reported scores are summed responses. For this measure, higher scores indicate a higher 'autistic load', meaning individuals are thought to be closer to the autistic end of the autism spectrum. As expected, a significant group difference in SRS- and AQ-scores was observed (Table 5.2). These results support the clinical diagnosis all participants with ASD received prior to participation.

Table 5.2. Scores on scales measures autistic traits, depression, anxiety, and alexithymia

	ASD				NT				Difference	
	Mean	Min	Max	SD	Mean	Min	Max	SD	T	p
SRS	60.89	40	78	10.97	49.74	40	60	6.04	3.86	**0.0005**
AQ	123.33	95	153	15.29	103.53	81	127	13.04	4.25	**0.0002**
BDI	11.83	0	27	8.82	6.37	2	24	5.01	2.33	**0.0255**
STAI	41.94	21	73	13.17	32.95	23	51	7.47	2.57	**0.0145**
TAS	52.06	24	69	12.34	45.05	34	62	8.86	1.99	0.0543

Note. Abbreviations. SRS: Social Responsiveness Scale. AQ: Autism quotient. BDI: Beck Depression Questionnaire. STAI: State-Trait Anxiety Inventory. TAS: Toronto Alexithymia Scale.

2.1.2. Screening questionnaires

To investigate the groups regarding depression and anxiety, participants completed a Dutch version of the Beck Depression Inventory (BDI-II-NL) (Beck et al., 1996; Van der Does,

2002) and a Dutch version of the State-Trait Anxiety Inventory for adults (STAI DY2) (Spielberger, 1983; Van der Ploeg, 1982). Individuals with ASD scored significantly higher on both the anxiety and the depression questionnaire, indicating higher levels of (pre-clinical) depression and anxiety in the ASD group (Table 5.2). This finding is in line with research showing high prevalence rates of up to 30% for anxiety and depression in the ASD population, with lifetime prevalence rates even reaching 77% (Croen et al., 2015; Joshi et al., 2013). Other medical and psychiatric illnesses are also found to be more common in the ASD population compared to the general population (Croen et al., 2015). Hence, our finding seems in line with the literature and – regrettably - inherent to the studied population.

In addition, a Dutch version of the Toronto Alexithymia scale (TAS-20) was administered (Bagby et al., 1994; Trijsburg et al., 1997). This 20-item scale measures self-reported symptoms of alexithymia, among which are problems with recognising and expressing emotions (Taylor, 1984). Higher scores on the TAS-20 indicate more and/or more severe self-reported alexithymia symptoms. Results on the TAS show a close-to-significant difference between the groups (Table 5.2), indicating that individuals with ASD are characterised by more and/or more severe problems with recognising and expressing emotions. However, the difference between the groups does not reach significance. Our finding is not surprising, as the general literature reports high levels of alexithymia in the ASD population (Poquérusse et al., 2018). Furthermore, recent research has reported a consistent link between higher levels of alexithymia and depression and anxiety in ASD (Bloch et al., 2021; Fietz et al., 2018; Morie et al., 2019; Oakley et al., 2020), indicating alexithymia might play a mediating role in the high prevalence of depression and anxiety in the ASD population.

2.2. Multimodal Emotion Recognition Test (MERT)

The Multimodal Emotion Recognition Test (MERT) (Bänziger et al., 2009) was developed to measure emotion recognition abilities across different modalities and expressions. More specifically, it tests the visual and auditory ability of participants to indicate which emotion is expressed by an actor, including anger, anxiety, contempt, despair, disgust, elated joy, fear, happiness, irritation, and sadness. Expressions are demonstrated in four different modalities: static pictures, dynamic clips without sound, dynamic clips with sound, and sound only. A total of 120 items is presented, with 30 items in every modality. The MERT

was used because the current study was part of a larger project focussing on emotion processing in ASD, including vocal emotion processing.

2.3. Oddball paradigms

2.3.1. Facial identity oddball paradigm

2.3.1.1. Stimuli

Stimuli were used in previous research (Liu-Shuang et al., 2014; Vettori, Dzhelyova, et al., 2019) and displayed full-front, coloured images of 25 male and 25 female faces with a neutral expression. Photographs were taken under standardised conditions. Faces were isolated by cropping external features (e.g., hair, ears). Images had a width of 316 ± 19 pixels and a height of 425 pixels. Inverted faces were created by flipping all images vertically. Stimuli were presented at a distance of 80 cm, with a visual angle of approximately 7.15° x 5.01°. During stimulation, the average luminance of the faces was equalised.

2.3.1.2. Design

The design was similar to previous studies (Dwyer et al., 2019; Liu-Shuang et al., 2014; Vettori, Dzhelyova, et al., 2019). Baseline images (i.e., faces with a fixed identity) were presented at a rapid frequency of 6 Hz, periodically interleaved by oddball images (i.e., faces with different identities) every fifth image (1.2 Hz) (Figure 5.1). Faces were presented upright or inverted in separate sequences. In addition, a fixation cross was placed either on the eye region or on the mouth region. All combinations of these presentations yielded four presentation-conditions: upright-eyes, upright-mouth, inverted-eyes, inverted-mouth. Each condition was presented in two sequences (one with male faces, one with female faces), with a total of eight acquired sequences. Every sequence started with a blank screen lasting two to five seconds and two seconds of fade-in, followed by 40 seconds of stimulus presentation and two seconds of fade-out. Throughout the sequence, the size of the presented faces changed continuously to prevent participants from relying on low-level visual features to discriminate between faces, and instead rely on higher-level face processing.

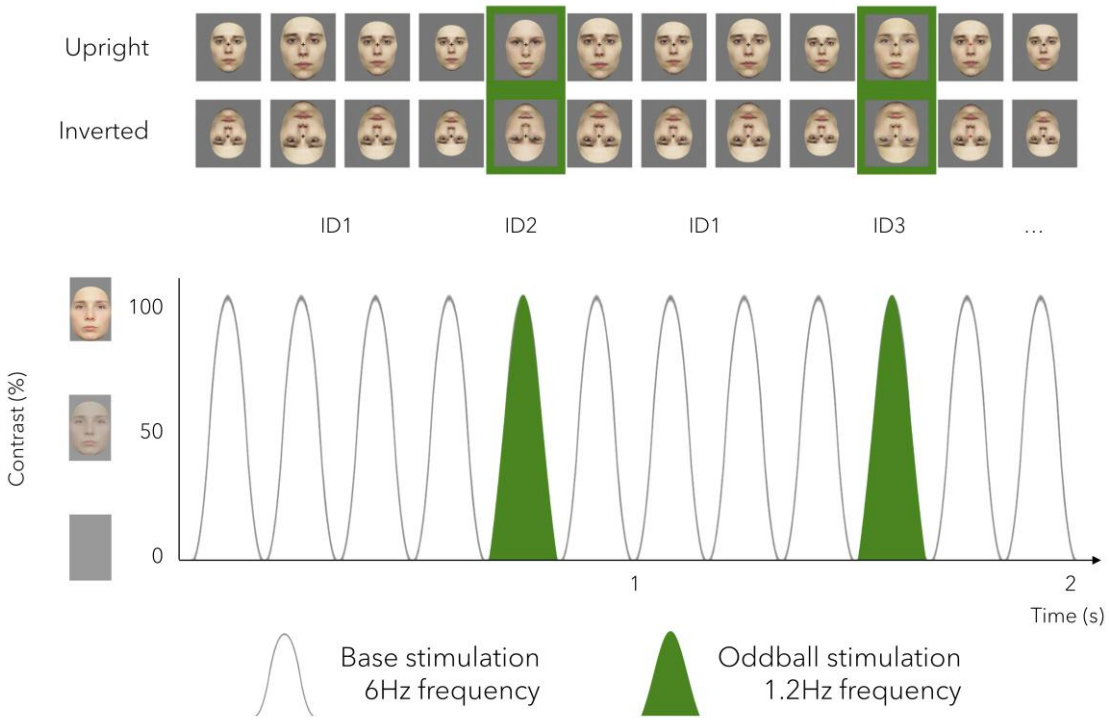


Fig 5.1. Identity oddball paradigm. Sequences of faces of the same identity were presented at a base rate of 6 Hz, interleaved with a face of a different identity every fifth stimulus, i.e., at the 1.2 Hz oddball rate (oddball presentation shown in green). Upright and inverted faces were presented in separate sequences, which were repeated four times each: two times with fixation cross on the eye region, two times with the fixation cross on the mouth region. Shown here are upright and inverted stimuli with a fixation cross on the eye region.

2.3.2. Facial expression oddball paradigm

2.3.2.1. Stimuli

Stimuli were previously used (Van der Donck et al., 2020) and included neutral and expressive full front faces of seven males and seven females from the Karolinska Directed Emotional Faces Database (Lundqvist et al., 1998). Expressive stimuli included angry, fearful, sad, and happy faces. The size of every image was set to 360 x 540 pixels. Stimuli were presented at a distance of 80 cm, with a visual angle of approximately 6.44° x 5.08°. During stimulation, the average luminance and contrast of the faces was equalised.

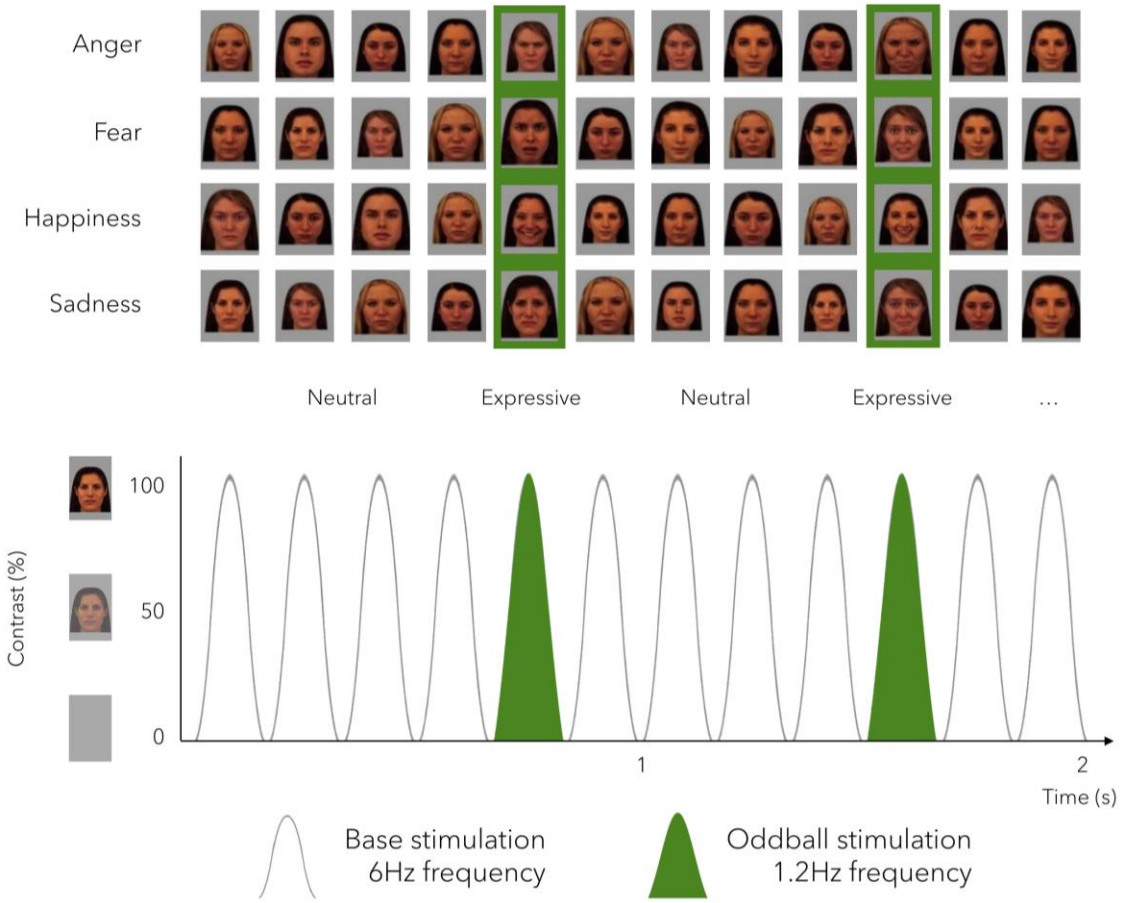


Figure 5.2. Expression oddball paradigm. A stream of neutral faces was presented at a base rate of 6 Hz, interleaved with an expressive face (angry, fearful, sad, or happy) every fifth stimulus, i.e., at the 1.2 Hz oddball rate (oddball presentation shown in green). Every expression was presented in a separate sequence, which was repeated four times. Identity and size of the faces changed every image.

2.3.2.2. Design

The design was similar to previous studies (Dzhelyova et al., 2017; Poncet et al., 2019; Van der Donck et al., 2020). Baseline images (i.e., neutral faces) were presented at a rapid frequency of 6 Hz, periodically interleaved with oddball images (i.e., expressive faces) every fifth image (1.2 Hz) (Figure 5.2). Oddball images were presented in four expressions yielding four conditions: anger, fear, happiness, and sadness. Every condition was presented in four sequences (two with male faces, two with female faces), with a total of sixteen acquired sequences in randomised order. Every sequence started with a blank screen lasting two to five seconds and two seconds of fade-in, followed by 60 seconds of

stimulus presentation and two seconds of fade-out. A fixation cross was presented on the nasion of the face. Throughout the sequence, the identity and size of faces continuously changed to prevent participants from relying on low-level visual features to discriminate between expressions, and instead rely on higher-level face processing.

2.3.3. Orthogonal fixation cross task

Both oddball paradigms included an orthogonal task to ensure participants were paying attention to the images. Ten times within every sequence, the fixation cross changed colour from black to red. This change in colour was brief (300 ms) and occurred randomly. Participants were instructed to press a button in response to this change in colour, as accurately and fast as possible.

2.4. EEG acquisition.

EEG activity was recorded using a BIOSEMI Active-Two amplifier system with 64 Ag/AgCl electrodes and two additional electrodes as reference and ground electrodes. EEG was recorded at 512 Hz.

2.5. EEG analysis.

All EEG analyses were performed using Letswave 6 (http://nocions.webnode.com/letswave) and MATLAB 2020b (The Mathworks Inc., 2020). Further statistical analyses were performed in MATLAB 2020b (The Mathworks Inc., 2020) and R (R Core Team, 2020), using packages 'Afex' (Singmann et al., 2021) and 'emmeans' (Lenth, 2021).

2.5.1. Pre-processing

A first step involved pre-processing of the data. Data was cropped into segments containing one sequence, as one sequence contained one condition. Next, a bandpass filter was applied to exclude irrelevant information, after which down sampling was performed to reduce the workload on the computer while keeping sufficient data points. Noisy channels were re-estimated by interpolating the three spatially nearest electrodes, which was necessary for seven participants in the identity paradigm (2 NT, 5 ASD) with an

average of 0.2 re-estimated channels for every participant; and for twelve participants in the expression paradigm (5 NT, 6 ASD) with an average of 0.5 re-estimated channels for every participant. A correction for eye blinking was applied using independent component analysis (ICA) in three participants (1 NT, 2 ASD) for the identity paradigm and four participants (2 NT, 2 ASD) for the expression paradigm, as these participants blinked more than two standard deviations above average. Finally, all segments were re-referenced to a common average reference and cropped to start immediately after fade-in and contain an integer number of 1.2 Hz cycles. More specifically, data were cropped into segments of 39.97 seconds and 48 cycles for the identity paradigm and 59.87 seconds and 72 cycles for the expression paradigm.

2.5.2. Frequency domain analysis

Next, we ran a frequency domain analysis. For this analysis, we averaged the data across epochs in the time domain for every condition (i.e., for all upright and all inverted epochs in the identity paradigm, and for every separate expression in the expression paradigm) and for each participant. On the time-averaged data, a fast Fourier transformation (FFT) was applied, allowing us to look at signals in the frequency domain. Using this technique, we expected the EEG data to contain signals at frequencies that are harmonics (i.e., integer multiples) of the base (6 Hz) and oddball frequencies (1.2 Hz). An oddball EEG response at 1.2 Hz and its harmonics appears only if the brain can consistently differentiate between base and oddball stimuli. Therefore, the oddball EEG response objectively quantifies the neural sensitivity to automatically detect changes in facial identity and facial expression, respectively yielding an identity discrimination response and an expression discrimination response. Note that the 'expression discrimination response' does not strictly refer to a distinction between different expressions, but rather to a distinction between neutral and expressive faces. Nonetheless, we will use 'expression discrimination response' for the sake of simplicity and consistency with earlier studies.

We used the amplitudes at the oddball frequency and its harmonics as a measure of facial identity and expression discrimination (Dzhelyova et al., 2017; Liu-Shuang et al., 2014). Moreover, we computed two measures to interpret our results: (1) a signal-to-noise ratio (SNR) by dividing the amplitude of a frequency bin of interest by the average amplitude of the 20 surrounding frequency bins (Rossion et al., 2012), and (2) a baseline-corrected amplitude by subtracting the average amplitude of the 20 surrounding frequency bins from

the amplitude of a frequency bin of interest (Retter & Rossion, 2016). The 20 surrounding frequency bins consist of ten bins on each side of the bin of interest, but excluding the two immediately neighbouring and two most extreme bins. For visualisation, we used SNR spectra, as small amplitude responses in high frequency ranges can still have a high signal-to-noise ratio. The second measure, baseline corrected amplitude, was used to statistically quantify the base and oddball responses.

To determine the range of base and oddball harmonics to include in further analyses, we assessed which of the harmonics reached amplitudes above noise-level. For this purpose, Z-scores were calculated for the identity and the expression paradigm separately (Liu-Shuang et al., 2014). More specifically, we averaged FFT amplitude spectra across subjects within the ASD and the NT group, and next across all the electrodes and across all the electrodes in regions of interest for every condition in both paradigms: upright and inverted sequences for the identity paradigm, and the four separate expressions in the expression paradigm. We then computed z-scores using mean and standard deviation of the 20 bins surrounding the bin of interest (i.e., harmonics of base and oddball frequency). Harmonics were included in further analyses if the Z-scores for two consecutive harmonics were above 1.64 ($p < .05$, one-tailed) in both groups and across all conditions. Significant harmonics were computed separately for base and oddball responses as well as for the identity and expression paradigm. In both paradigms, we quantified the base response as the sum of the responses of the first three harmonics (i.e., until 3F = 18 Hz). For the identity paradigm, the oddball responses were quantified as the summed responses of the first four harmonics. For the expression paradigm, we quantified the oddball response as the summed responses of the second, third and fourth harmonics (Retter & Rossion, 2016).

2.5.3. Determination of regions of interest

Regions of interest (ROIs) were defined based on previous findings and visual inspection of the topographical maps. Previous research using these paradigms has consistently yielded three regions of interest: the left and right occipitotemporal cortices (LOT and ROT) and the medial occipital (MO) cortex (Dzhelyova & Rossion, 2014b, 2014a; Liu-Shuang et al., 2014, 2016; Rossion et al., 2015; Van der Donck et al., 2020; Vettori, Dzhelyova, et al., 2019). The LOT and ROT ROIs were defined by averaging the three electrodes with the highest summed baseline-corrected oddball response within each of the respective hemispheres across all conditions and both groups. This yielded the same regions of

interest for both the identity and the expression paradigm: an LOT region comprising channels P7, P9 and PO7; and an ROT region consisting of channels P8, P10 and PO8. The MO region was defined by averaging the two channels with the highest response at 6 Hz, comprising channels Iz and Oz in both paradigms.

2.5.4. Statistical analyses

Accuracy and reaction times on the orthogonal task in both paradigms were analysed using R (R Core Team, 2020). For the calculation of reaction times, trials without a response were excluded. Overall accuracy and reaction time across conditions were compared between groups. The assumption of equal variances was met. Differences between the groups regarding overall accuracy on the orthogonal tasks were tested using a Wilcoxon test, as data did not meet the normality assumption. Group-differences in overall reaction times were studied using a two-sample t-test.

Using FPVS-EEG, we investigated the neural sensitivity to different facial identities (for the facial identity paradigm) and to different facial expressions (for the facial expression paradigm). For this purpose, we applied linear mixed models on the baseline-corrected amplitudes (package 'Afex': Singmann et al., 2021). Dependent variables were either base or oddball responses of the identity or expression paradigm, as separate models were fitted, with a total of four models. For the *identity base responses*, we fitted a linear mixed model with Group (ASD versus TD) as a fixed between-subject factor, and Orientation (inverted versus upright) and ROI (LOT, MO, ROT) as fixed within-subject factors. For the *identity oddball responses*, we fitted a linear mixed model with Group (ASD versus TD) as a fixed between-subject factor, and Orientation (inverted versus upright) and ROI (LOT, ROT) as fixed within-subject factors. For the *expression base responses*, we fitted a linear mixed model with Group (ASD versus TD) as a fixed between-subject factor, and Emotion (Anger, Fear, Happy, Sad) and ROI (LOT, MO, ROT) as fixed within-subject factors. For the *expression oddball responses*, we fitted a linear mixed model with Group (ASD versus TD) as a fixed between-subject factor, and Emotion (Anger, Fear, Happy, Sad) and ROI (LOT, ROT) as fixed within-subject factors. We accounted for repeated measures by including a random intercept for every participant. The Kenward-Roger method was used to calculate degrees of freedom. Post-hoc tests were applied when main or interaction effects were significant (package 'emmeans': Lenth, 2021) with a Bonferroni correction for multiple comparisons. Data were log-transformed to meet the assumption of normally distributed

residuals in all models, tested with a Shapiro-Wilk's test. Finally, we ran analyses with and without including lefthanded individuals (2 ASD), non-righthanded individuals (i.e., two lefthanded and two ambidextrous; 3 ASD, 1 NT) and individuals with comorbidities (four individuals with comorbid ASD - attention deficit (hyperactivity) disorder). As results were not influenced by the exclusion of these participants, we report results of analyses including all participants.

3. Results

3.1. Behavioural results

3.1.1. Emotion recognition test

We found no significant differences between the groups in terms of explicit behavioural emotion recognition (Table 5.3). Reported scores are percentages of correctly identified expressions, thus higher scores indicate a better recognition of emotional expressions. Results of the MERT show similar performances for both groups, across all modalities.

Table 5.3. Scores on Multimodal Emotion Recognition Test

	ASD				NT				Difference	
	Mean	Min	Max	SD	Mean	Min	Max	SD	T	p
MERT average	52.69	36.7	66.7	8.24	53.98	43.3	71.7	7.43	0.50	0.6192
MERT visual	56.84	40	80	10.38	59.46	46.7	73.3	8.76	0.83	0.4113
MERT audio	43.14	26.7	66.7	9.94	42.28	20	63.3	11.60	0.24	0.8109
MERT AV	61.30	40	80	11.62	63.34	46.7	83.3	8.60	0.61	0.5460
MERT picture	49.45	30	60	8.65	50.87	33.3	66.7	8.23	0.51	0.6104

Note. Abbreviations. MERT: Multimodal emotion recognition test. AV: audio-visual

3.1.2. Orthogonal task

No significant group differences were observed regarding overall accuracy and reaction times on the orthogonal fixation cross tasks. For the identity paradigm, we found no significant group differences regarding overall accuracy (M_{NT} = 96.81%, M_{ASD} = 96.48%, W = 200, p = 0.3829) and overall reaction times (M_{NT} = 412 ms, M_{ASD} = 423 ms, t_{35} = 1.43, p = 0.4245). Similarly, we found no significant differences between the groups regarding overall accuracy (M_{NT} = 93.74%, M_{ASD} = 95.97%, W = 123, p = 0.1488) and overall reaction times (M_{NT} = 456 ms, M_{ASD} = 455 ms, t_{35} = 0.62, p = 0.5395) in the expression paradigm.

These results show that the orthogonal task was performed fast with a high level of accuracy in both groups, indicating all participants were following instructions and paying attention to the fixation cross.

3.2. Results of the facial identity FPVS-EEG paradigm

3.2.1. Similar base rate responses in ASD and NT

General visual base rate responses were clearly visible in both groups, as shown by peaks in the SNR spectrum at the base rate of 6 Hz and its harmonics (Figure 5.3.A). The visual base rate response was most pronounced over the medial occipital (MO) region, as shown on topographical maps (Figure 5.3.B). Indeed, a highly significant main effect of ROI was observed ($F_{2,175}$ = 179.67, $p < 0.001$), with higher base rate responses in the MO region compared to the two more lateral regions ($t_{175} > 14.66$, $p_{bonf} < 0.001$ in both cases) (Figure 5.3.C). In addition, we observed higher base rate response in ROT compared to LOT (t_{175} = 3.07, p_{bonf} = 0.0074). We did not find a significant main effect of group, indicating both groups showed a similar neural synchronisation to FPVS of faces ($F_{1,35}$ = 0.01, p = 0.9260). In addition, we observed no main effect of orientation, indicating upright and inverted faces yielded a similar base rate response ($F_{1,175}$ = 0.31, p = 0.5754). Finally, no significant two- or three-way interactions were observed (Group x Orientation: $F_{1,175}$ = 2.17, p = 0.1429; ROI x Orientation: $F_{2,175}$ = 0.42, p = 0.6566; Group x ROI: $F_{2,175}$ = 2.62, p = 0.0758; Group x ROI x Orientation: $F_{2,175}$ = 0.32, p = 0.7244).

3.2.2. Similar identity discrimination responses in ASD and NT

Neural sensitivity to changes in facial identity was investigated using the responses tagged to the oddball rate. SNR spectra clearly show the facial identity discrimination responses in both groups as peaks at the oddball rate of 1.2 Hz and its harmonics (Figure 5.4.A). These responses were distributed mostly across bilateral occipitotemporal regions (LOT and ROT), with a right-hemispheric dominance (Figure 5.4.C). Indeed, a highly significant main effect of ROI was observed, with higher oddball responses in the ROT than the LOT region ($F_{1,105}$ = 14.18, $p < 0.001$).

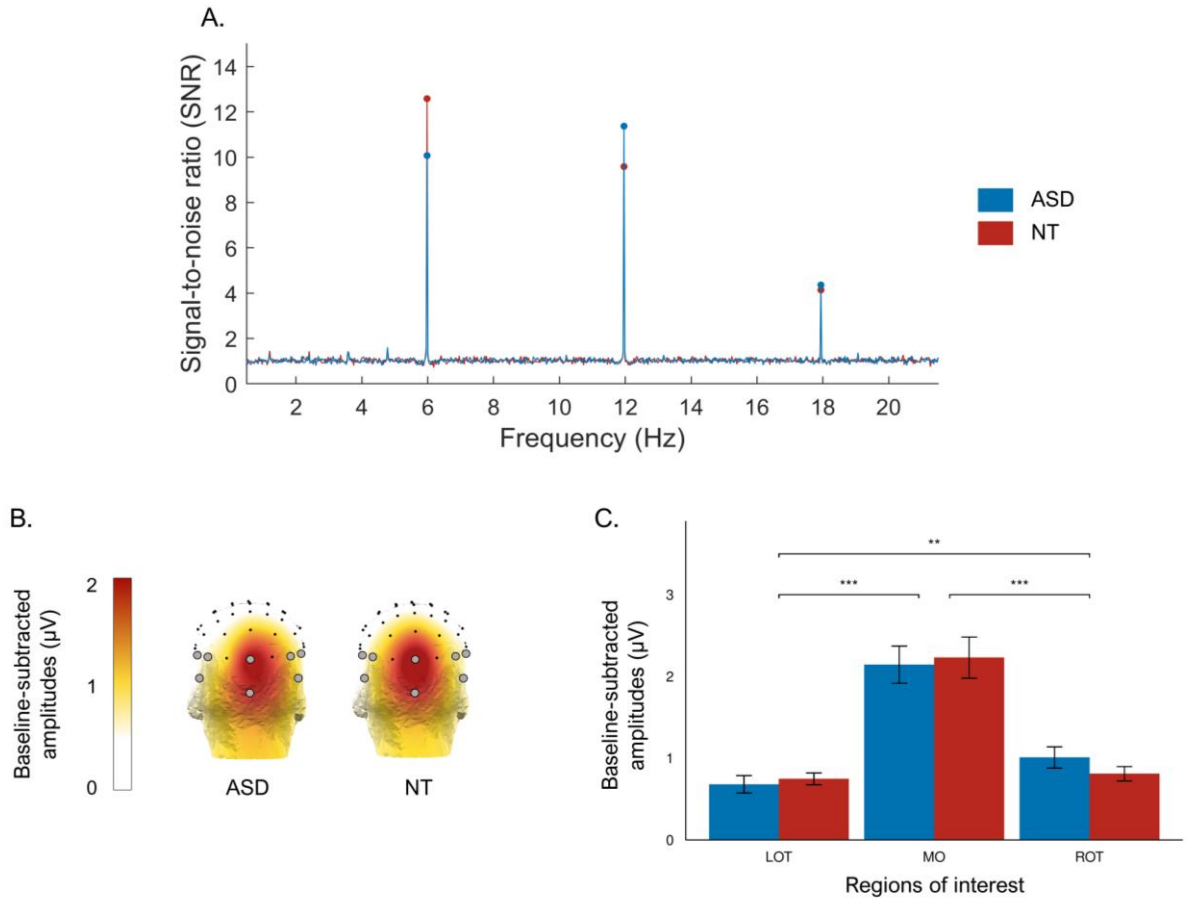


Figure 5.3. Base rate responses in the identity paradigm. A. Signal-to-noise (SNR) spectrum showing responses at base rate frequency (6 Hz) and its harmonics (12 and 18 Hz) for both groups. B. Topographies showing the distribution of base rate responses across the brain. Open dots demonstrate which electrodes are included in the three regions of interest. The left and right three-dot-configurations mark the left and right occipitotemporal regions (LOT and ROT), respectively. The two dots in the middle of the head illustrate the medial occipital region (MO), which is clearly dominant for the base rate responses. C. Bar graph showing the baseline-corrected amplitudes for all ROIs and both groups, including the main effect of ROI. Error bars demonstrate standard errors of the mean (SEM). Asterixis indicate p-values, with ** marking difference with $p < .01$, and *** marking differences with $p < .001$.

In addition, we observed a significant main effect of orientation, demonstrating a face-inversion effect with larger responses for upright than inverted faces ($F_{1,105} = 27.80$, $p < 0.001$). We did not find a significant main effect of group ($F_{1,35} = 0.08$, $p = 0.7824$), indicating oddball responses were similar in both groups (Figure 5.4.B). In addition, we observed no significant two-way interactions, indicating a similar face inversion effect in both groups (Group x Orientation: $F_{1,105} = 0.62$, $p = 0.4330$) and both ROIs (ROI x

Orientation: $F_{1,105}$ = 0.16, p = 0.6866), as well as a similar right-hemispheric dominance in both groups (Group x ROI: $F_{1,105}$ = 1.70, p = 0.1955). Finally, the three-way interaction between group, orientation and ROI was not significant ($F_{1,105}$ = 0.96, p = 0.3294).

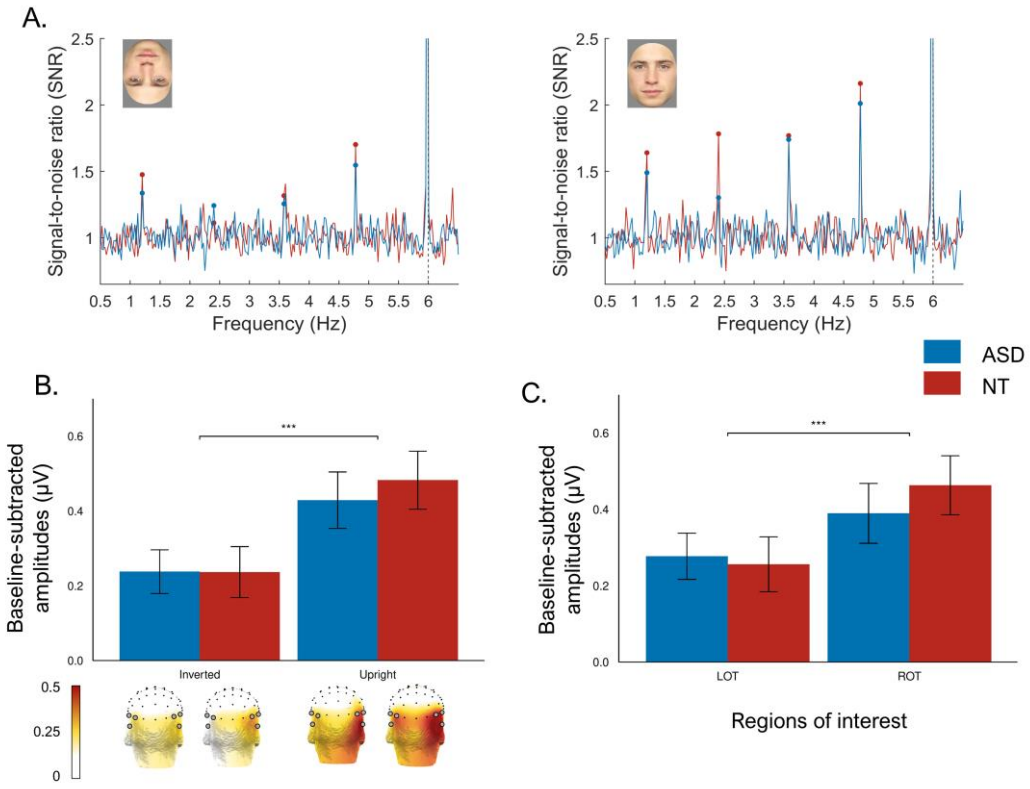


Figure 5.4. Oddball responses indexing automatic neural facial identity discrimination. A. Signal-to-noise (SNR) spectra showing responses at oddball rate frequency (1.2 Hz) and its harmonics (2.4, 3.6 and 4.8 Hz) for both groups and both conditions. B. Bar graph displaying the baseline-corrected amplitudes for both orientations and groups, showing the main effect of orientation (i.e., face inversion effect). Topographies show the distribution of oddball responses across the brain. Open dots demonstrate electrodes that constitute the regions of interest. The left and right three-dot-configurations mark the left and right occipitotemporal regions (LOT and ROT), respectively, and an ROT dominance is demonstrated. C. Bar graph showing the baseline-corrected amplitudes for both ROIs and both groups, demonstrating the main effect of ROI. Error bars demonstrate standard errors of the mean (SEM). Asterixis indicate p-values, with *** marking differences with p < .001.

3.3. Results of the facial expression FPVS-EEG paradigm

3.3.1. Similar base rate responses in ASD and NT

General visual base rate responses were clearly visible in both groups, as shown by peaks in the SNR spectrum at the base rate of 6 Hz and its harmonics (Figure 5.5.A).

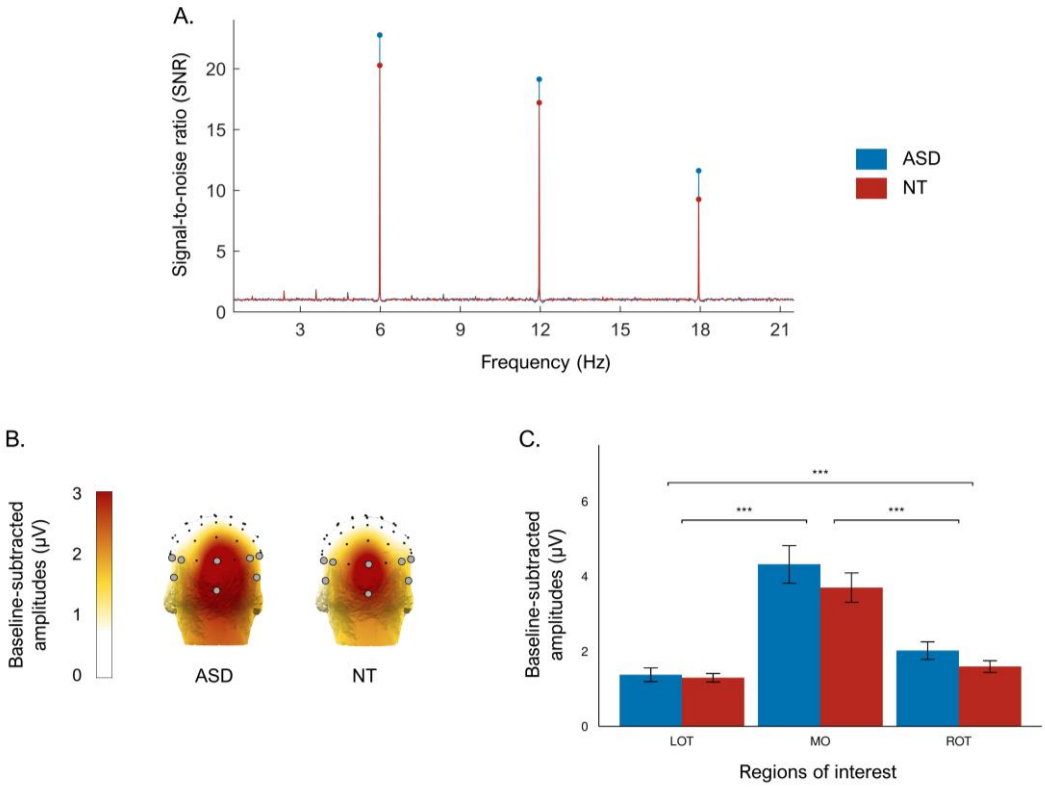


Figure 5.5. Base rate responses in the expression paradigm. A. Signal-to-noise ratio (SNR) spectrum showing responses at the base rate frequency (6 Hz) and its harmonics (12 and 18 Hz) for both groups. B. Topographies showing the distribution of base rate responses across the brain. Open dots demonstrate electrodes that constitute the regions of interest. The left and right three-dot-configurations mark the left and right occipitotemporal regions (LOT and ROT), respectively. The two dots in the middle of the head illustrate the medial occipital region (MO), which is clearly dominant for the base rate responses. C. Bar graph showing the baseline-corrected amplitudes for all ROIs and both groups, showing the main effect of ROI. Error bars demonstrate standard errors of the mean (SEM). Asterixis indicate p-values, with *** marking differences with $p < .001$.

The base rate responses were distributed mostly over the medial occipital (MO) region, as shown on topographical maps (Figure 5.5.B). Indeed, a highly significant main effect of ROI was observed ($F_{2,385}$ = 424.90, p < 0.001), with higher base rate responses in the MO region compared to the other regions (t_{385} > 21.27, p < 0.001 in both cases) (Figure 5.5.C). In addition, we observed higher base rate responses in ROT compared to LOT (t_{385} = 6.63, p < 0.001). We observed no main effect of group ($F_{1,35}$ = 1.05, p = 0.3117) nor emotion ($F_{3.385}$ = 0.09, p = 0.9641), indicating the base rate responses were similar across groups as well as expressions. Finally, no significant two- or three-way interactions were observed (Group x ROI: $F_{2,385}$ = 2.75, p = 0.0654; Group x Emotion: $F_{3,385}$ = 0.35, p = 0.7902; Emotion x ROI: $F_{6,385}$ = 0.07, p = 0.9984; Group x Emotion x ROI: $F_{6,385}$ = 0.01, p = 1).

3.3.2. Similar expression discrimination responses in ASD and NT

Automatic neural sensitivity to discriminate between neutral and expressive faces was investigated using the oddball responses. SNR spectra clearly show the facial expression discrimination responses in both groups as peaks at the significant harmonics of the oddball rate of 1.2 Hz (Figure 5.6). We observed a significant main effect of emotion ($F_{3,245}$ = 10.91, p < 0.001), with smaller responses to sad faces compared to all other expressions (t_{245} > 3.30, p < .0067 for all comparisons; Figure 5.7.A). The facial expression discrimination responses were distributed across bilateral occipitotemporal regions, with a slight right-hemispheric dominance (Figure 5.7.B), as evidenced by a significant main effect of ROI ($F_{1,245}$ = 4.06, p = 0.0450). We did not find a main effect of group ($F_{1,35}$ = 0.17, p = 0.6814), indicating that both groups showed similar oddball responses to expressive faces. In addition, we found no significant interactions, indicating a similar sensitivity to different expressions in both groups (Group x Emotion: $F_{3,245}$ = 1.22, p = 0.3030) and in both ROIs (ROI x Emotion: $F_{3,245}$ = 0.44, p = 0.7269), as well as a similar right-hemispheric dominance in both groups (Group x ROI: $F_{1,245}$ = 0.66, p = 0.4188). Finally, the three-way interaction between group, emotion and ROI was not significant ($F_{3,245}$ = 0.81, p = 0.4870).

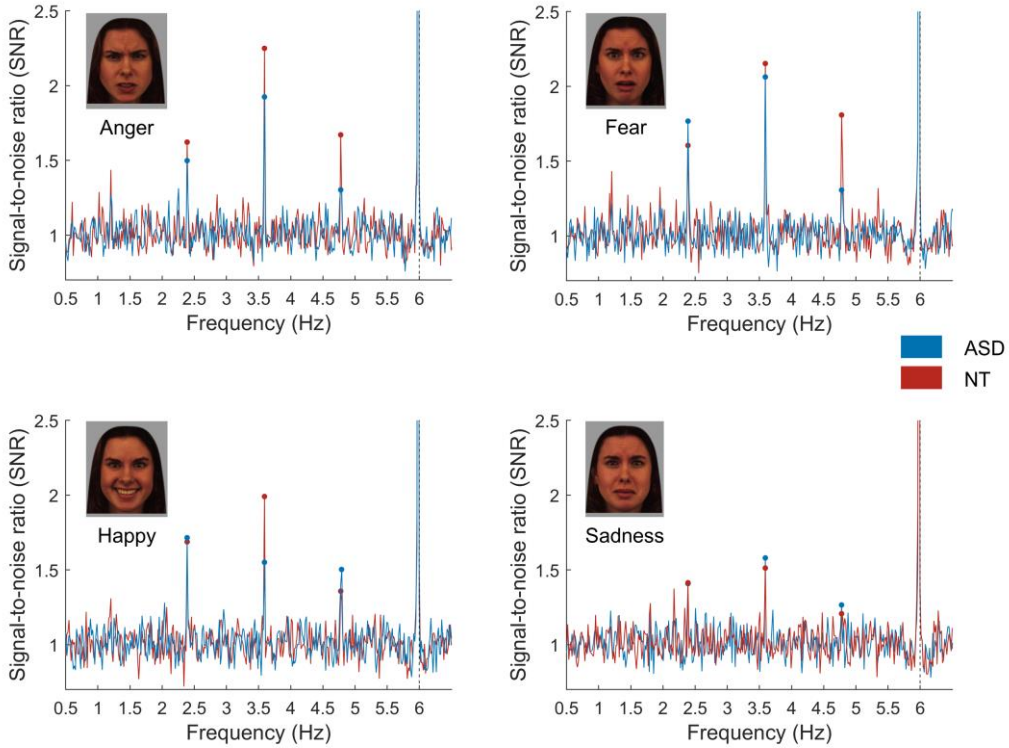


Figure 5.6. Spectral representations of expression discrimination responses, showing responses at significant harmonics of the oddball rate frequency (1.2 Hz) for both groups (2.4, 3.6 and 4.8 Hz).

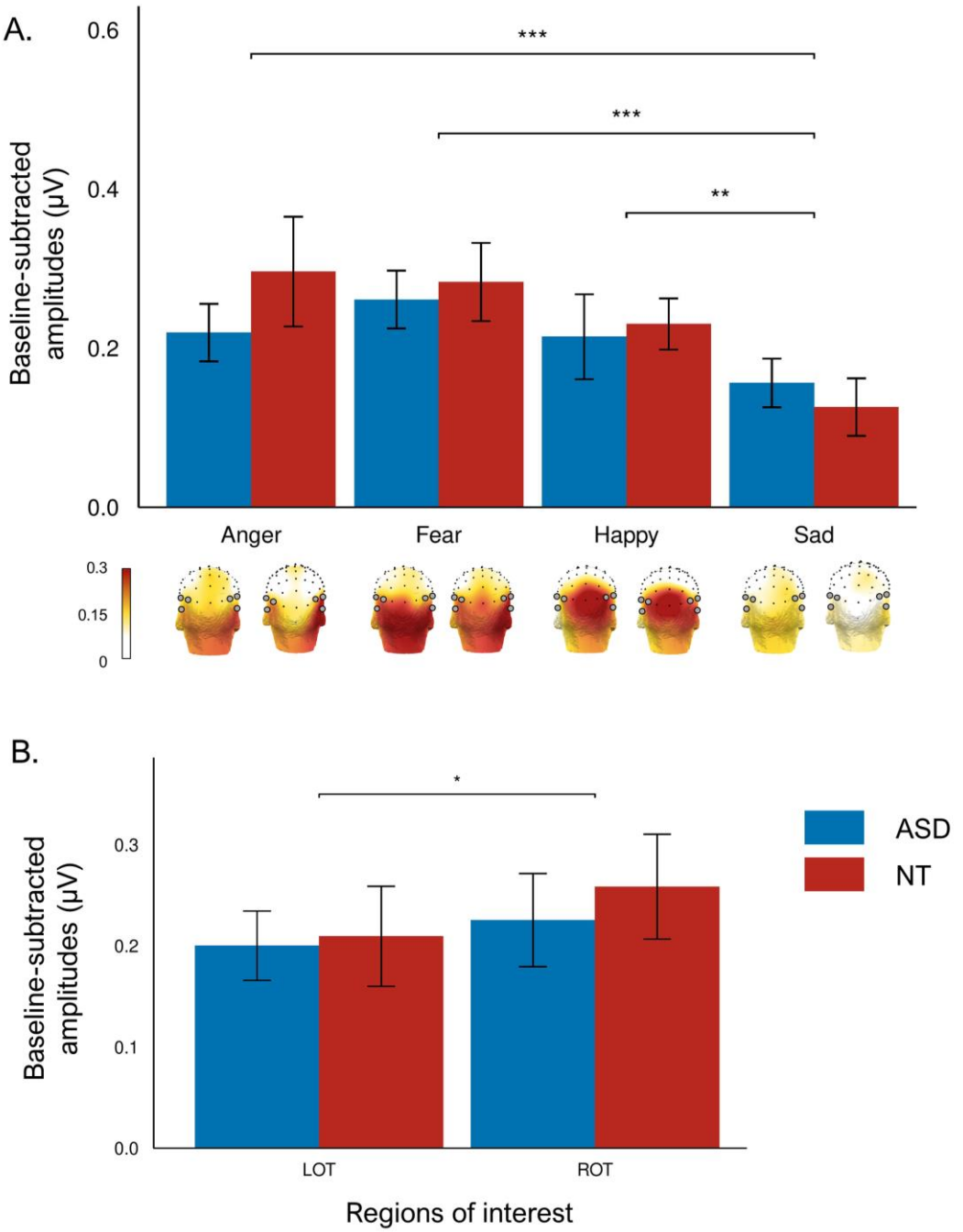


Figure 5.7. Oddball responses indexing automatic neural sensitivity to changes from neutral to expressive faces. A. Bar graph displaying the baseline-corrected amplitudes for all expressions and both groups, showing the main effect of emotion. Topographies show the distribution of expression discrimination responses across the brain. Open dots demonstrate electrodes that are part of regions of interest. The left and right three-dot-configurations mark the left and right occipitotemporal regions (LOT and ROT), respectively. B. Bar graph showing the baseline-corrected amplitudes for both ROIs and both groups, showing the main effect of ROI with a slight ROT dominance. Error bars demonstrate standard errors of the mean (SEM). Asterixis indicate p-values, with significant differences of: *** $p < .001$, ** $p < .01$, and * $p < .05$.

4. Discussion

4.1. Similar emotion recognition performance in adults with and without ASD

Our findings show that adult men with and without ASD performed very similar on the multimodal emotion recognition test (MERT). Both groups scored equally well across all modalities, indicating intact expression processing in individuals with ASD. Previous studies have not used the MERT to study facial expression processing is ASD. Nevertheless, two studies investigated how performance on the MERT relates to scores on different self-report instruments, among which one often-used self-administered instrument to measure autistic traits: the autism-spectrum quotient (AQ) (Alharbi et al., 2020; Palermo et al., 2018). No information was provided about the psychiatric or medical history of the adult sample of participants, but scores on the AQ indicate that most participants likely did not meet diagnostic criteria for ASD. A first study found that AQ-scores were not associated with MERT performance (Palermo et al., 2018), while the other reported a negative correlation indicating that individuals with a higher score on the AQ (more likely to have ASD) perform worse on the MERT (Alharbi et al., 2020). Our results are in line with the first study, as a sample of individuals diagnosed with ASD would be expected to have higher AQ-scores than the neurotypical group, while no significant differences in performance on the MERT were observed. However, although not significant, our ASD sample performed slightly worse across all modalities of the MERT, except the auditory modality. This indicates that there might indeed be a (modest) association between AQ- and MERT scores.

In general, past behavioural studies have often found facial expression processing to be atypical in individuals with ASD, especially adults (Harms et al., 2010; Uljarevic & Hamilton, 2013), although this finding is not consistent (Adolphs et al., 2001; Hendriks et al., 2021). Previous research demonstrating intact expression processing in ASD samples has typically been carried out in children and adolescents (e.g., McPartland et al., 2011) or used familiar faces as stimuli (e.g., Barton et al., 2004). Thus, our behavioural results are not at odds with the face expression processing literature in general but seem rather unique, especially for the adult ASD population studied here. Our findings could indicate that adults with ASD have learned to compensate for initial face processing difficulties (Harms et al., 2010). In

addition, it seems possible that we have recruited an unusually high functioning sample of individuals with ASD with exceptionally intact facial expression recognition.

4.2. Similar synchronisation to visual stimulation in adults with and without ASD

The base rate responses in both paradigms reflect the neural synchronisation to visual stimulation of faces in general. The base rate responses were similar for both groups in both paradigms, indicating a similar neural synchronisation to faces across groups. Base rate responses were found to be centred over the medial occipital (MO) region. Indeed, we found responses to be significantly higher in this region compared to the more lateral ROT and LOT, probably revealing the large involvement of early visual areas that are located in the medial occipital cortex. This finding is in line with previous studies in children and adults with ASD (Dwyer et al., 2019; Liu-Shuang et al., 2014; Vettori, Dzhelyova, et al., 2019). In addition, the similar neural synchronisation to same-identity faces in both groups suggests a similar habituation to faces in individuals with and without ASD. This contrasts with earlier studies that found reduced habituation to faces in adult and children with ASD (Ewbank et al., 2017; Swartz et al., 2013). However, like our findings, another study found similar adaptation to faces in adults with and without ASD (Hendriks et al., 2021).

4.3. Similar sensitivity to changes in facial identity in adults with and without ASD

Using EEG in combination with FPVS, we were able to investigate the neural sensitivity to automatically discriminate between different facial identities. An oddball response in the identity paradigm will only appear if the brain is able to consistently differentiate between different facial identities, thereby objectively quantifying the neural sensitivity to changes in facial identity. Indeed, identity discrimination responses were clearly present in the data in both groups, indicating that different identities are consistently discriminated within a single glance (note that every oddball face was presented less than 167 ms). Our findings show that the right hemisphere is dominant, as the signal is distributed mostly over the right occipitotemporal region. Right-sided dominance is a consistent finding in the study of face processing in children and adults (Dwyer et al., 2019; Haxby, Hoffman, et al., 2000; Rossion, Joyce, et al., 2003; Van der Donck et al., 2020; Vettori, Dzhelyova, et al., 2019).

However, this lateralised face processing response has been argued to be primarily present in males and to a lesser extent in females, who seem to process faces more bilaterally (Proverbio et al., 2006).

Importantly, no group differences were observed in terms of identity discrimination responses, implying that individuals with ASD are as sensitive as neurotypicals to changes in facial identity. This is not in line with general findings of impaired facial identity processing in individuals with ASD (Tang et al., 2015; Weigelt et al., 2012) and previous studies using the same paradigm in children (Vettori, Dzhelyova, et al., 2019). However, other studies have reported neural processing of facial identity to be similar in adults with and without ASD (Hendriks et al., 2021; Kleinhans et al., 2009). A developmental effect of facial identity processing might be at play.

We observed a significant face inversion effect in both groups, suggesting that the oddball responses in the upright condition indeed reflect high-level facial identity processing. This is in line with previous findings in adults (Liu-Shuang et al., 2014, 2016). Furthermore, we found a similar face inversion effect in both groups (i.e., no interaction between orientation and group), suggesting that holistic face processing at a perceptual level is intact in individuals with ASD. This contrasts with a small portion of previous research showing a diminished or absent face inversion effect in individuals (mostly children) with ASD, frequently explained by impaired holistic processing (McPartland et al., 2004; McPartland, Webb, et al., 2011; O'Brien et al., 2014; Vettori, Dzhelyova, et al., 2019). However, our findings are in line with the general literature, in which the face inversion effect is often found to be similar in individuals with and without ASD (Weigelt et al., 2012), which is in line with the 'enhanced perceptual functioning' theory (Mottron et al., 2006). In particular, our results are similar to a study using an almost identical facial identity FPVS-EEG paradigm in adults with and without self-diagnosed ASD, in which an intact face inversion effect in ASD was also observed (Dwyer et al., 2019).

4.4. Similar sensitivity to changes from neutral to expressive faces in adults with and without ASD

We investigated the neural sensitivity to changes from neutral to expressive faces using EEG in combination with FPVS. An oddball response in this paradigm will only appear if the brain is able to consistently differentiate between neutral and expressive faces. Expression discrimination responses were clearly present in both groups, indicating that facial

expressions are consistently discriminated from neutrality within a single glance. Our findings show that the right hemisphere is dominant, as the signal is distributed mostly over the right occipitotemporal region (ROT). This is a consistent finding in the study of facial expression processing (Gainotti, 2019; Van der Donck et al., 2020), although -as mentioned before- this can possibly be attributed to the large overrepresentation of males in ASD research (Proverbio et al., 2006).

No significant differences between the groups were observed when comparing the expression discrimination responses, suggesting that individuals with ASD are as sensitive as neurotypicals to changes from neutral to expressive faces. While studies have reported intact facial expression processing in adults with ASD (Adolphs et al., 2001; Hendriks et al., 2021), this finding is not in line with general findings of impaired facial expression processing in individuals with ASD (Harms et al., 2010; Uljarevic & Hamilton, 2013). Accordingly, our findings contrast with findings of robust group differences in studies using the same EEG-FPVS paradigm in children (Van der Donck et al., 2020). It is possible that implicit face expression processing in indeed intact in adults with ASD, and that using this paradigm enabled us to make this observation without the interference of task demands or compensatory strategies. Furthermore, we observed a similar trend in expression discrimination responses to angry faces than in the study using the same paradigm in children (Van der Donck et al., 2020). Adult men with ASD, as boys with ASD, seem slightly less sensitive to discriminate angry faces rapidly and implicitly from neutral faces, although the group difference did not reach significance in adults. This group difference might be explained by a selective avoidance of angry faces throughout development in individuals with ASD (García-Blanco et al., 2017; Wang et al., 2018), which resonates with the active avoidance account of ASD-related atypicalities in face processing (Kylliäinen & Hietanen, 2006; Richer, 1976).

All facial expressions, except sadness, yielded expression discrimination responses of a similar size. We found a significantly lower oddball response to sad faces compared to other expressions, indicating that sad faces are processed as being less distinct from the neutral base stimuli compared to angry, fearful, and happy faces. This is in line with previous results of the same paradigm in children (Van der Donck et al., 2020). It might be argued that low-level perceptual features play a role. However, Van der Donck and colleagues (2020) provide convincing evidence against this argument. They calculated image-based differences between every expressive face and its neutral equivalent, showing that only happiness was more distinct from neutrality than other expressions. Hence, our

results cannot be explained by low-level stimulus characteristics. Another possible explanation entails a lack of salient, characteristic facial features in the facial expression of sadness. Indeed, research suggests that sadness is among the most difficult expressions to recognise (Gao & Maurer, 2009; Holland et al., 2019; Leppänen & Hietanen, 2004). Moreover, in a typical population behavioural evidence also shows that detection of sad faces among neutral faces is more challenging than detection of happy, angry, or fearful faces, as indicated by a lower accuracy and higher response times (Calvo & Nummenmaa, 2008). This is in line with our findings of reduced expression discrimination responses to sad faces. We could speculate that the fast presentation rates of our FPVS paradigm put the neural system under pressure, affecting the 'weakest' link first: the detection of a sad face among a stream of neutral faces.

4.5. Limitations and future directions

In the current study, the studied sample is rather small, especially to demonstrate the absence of an expected group difference. Due to the COVID-19 pandemic, recruitment was challenging, as participants were generally not eager to spend an entire day at the hospital to participate in scientific research. We plan to meet this limitation by continuing the recruitment until we reach approximately 25 individuals in every group.

The groups were successfully matched regarding age and IQ but might not be optimally comparable. First, handedness is suggested to influence the lateralisation of neural face processing responses (Brewster et al., 2011; Frässle et al., 2016). Therefore, it would have been preferable to either include only righthanded individuals or include the same amount of lefthanded individuals in both groups. In this study, two lefthanded individuals were part of the ASD group, with none in the NT group. To ensure handedness was not driving any of the results, analyses were performed with and without inclusion of the non-righthanded individuals. We adopted the same strategy for four individuals with a comorbid attention deficit (hyperactivity) disorder in the ASD group. We decided to include individuals with a double diagnosis in this study, as comorbidities are inherent to the ASD population. Indeed, comorbidities of ASD and ADHD are highly prevalent (Antshel et al., 2013, 2016; Lugo-Marín et al., 2019). Importantly, results were not influenced by handedness or comorbidities, and reported results included all participants.

This study included only male participants. For future studies, it would be interesting as well as important to also incorporate female subjects. Girls and women are often overlooked in

ASD research, although they are also - albeit less frequently - diagnosed with ASD. In addition, the sample included in this study entails mostly high functioning individuals with ASD, hindering generalisability of the results to the ASD population as a whole. In this study, we might have to consider the impact of the COVID-19 pandemic to account for the overrepresentation of high functioning individuals in our sample. The strain of ever-changing measures to prevent the virus from spreading might have severely impacted individuals with ASD, even more so than neurotypical individuals. Accordingly, it is likely that individuals with ASD that we found willing to participate were exceptionally well adapted and high functioning. In the future, FPVS-EEG can be helpful to avoid overrepresentation of high functioning individuals with ASD, because it is fast to acquire and there is no need to lay still for a long period of time (as is the case with MRI), this technique can be used to study (sub)populations that are challenging to include. More specifically, this means individuals with a 'higher autistic load' (i.e., more severe autistic symptoms) and individuals with a lower IQ can more easily be included in studies, which would permit researchers to make more general conclusions about a broader, more heterogeneous group of individuals with ASD.

In the current study, we did not administer a behavioural task to investigate facial identity recognition, hindering the comparison of behavioural and neural facial identity results. Behavioural and neural measures of facial identity processing do not seem to be particularly linked to one another in adult ASD populations (Tavares et al., 2016; Webb et al., 2012). Furthermore, when studying facial identity using FPVS paradigms, group differences in neural functioning in the absence of behavioural differences, as well as the opposite, have been observed (Dwyer et al., 2019; Vettori, Dzhelyova, et al., 2019). Hence, although performance on a behavioural facial identity task would have been preferable, its absence does not necessarily pose a problem.

The paradigms used in this study were the same as paradigms used in earlier studies investigating children with and without ASD (Van der Donck et al., 2020; Vettori, Dzhelyova, et al., 2019). Unexpectedly, we did not observe the same differences between individuals with and without ASD, as our findings in adults did not show significant differences between the groups. Therefore, it would be interesting to check whether the results from the FPVS-EEG studies in children can be replicated within the same population, to examine the robustness of the FPVS-EEG findings in children. Preliminary findings from a replication of the FPVS-EEG expression paradigm in our research group indicate that children with and without ASD indeed differ in terms of expression discrimination responses. The replication

of FPVS-EEG results in children would allow us to argue that the brains of adults with ASD function more like their neurotypical counterparts than is the case for children.

Finally, in the current study, we only investigated four basic facial expressions: anger, fear, happiness, and sadness. As everyday life exposes us to more expressions, it would be interesting to study whether and how adults with and without ASD differ regarding other and more complex emotions, with the added benefit of a higher ecological validity. In addition, facial expression processing research has mostly examined high intensity facial expressions, although some studies have used various levels of expression intensity (Evers et al., 2015; Griffiths et al., 2019; Law Smith et al., 2010). Future studies could also include expressions with varying intensities, again with the advantage of a higher ecological validity.

4.6. Conclusion

To summarise, no differences were found between high functioning adult men with ASD and age- and IQ-matched controls regarding behavioural facial expression processing, general neural synchronisation to a stream of faces, implicit and automatic neural sensitivity to fast changes in facial identity, and fast changes from neutral to expressive faces. In sum, our findings indicate that adults with ASD do not differ from their neurotypical counterparts in terms of facial identity and expression processing. Our results contrast the general face processing literature, and in particular earlier studies using the same paradigm in children. This contradiction might demonstrate the heterogeneity of the ASD population, of which we recruited a relatively high functioning sample. In addition, as our results are in line with an earlier study using a similar paradigm in adults, it might suggest that adults with ASD have learned to compensate for possible early-life difficulties in face processing.

Chapter 6

General discussion on face processing in ASD

Summary Chapter 6

In the second part of this dissertation, fMRI and EEG were used to investigate face processing in high functioning adult men with and without ASD. In Chapter 3, I provided some background about face processing, autism spectrum disorder (ASD) and ASD-related atypicalities in face processing. In Chapter 4, fMRI was used to investigate facial identity and expression processing in young adults with and without ASD, utilising a single paradigm involving dynamic facial stimuli. In Chapter 5, EEG was used to study facial identity and expression processing in adults with and without ASD, this time applying two separate paradigms (i.e., an identity paradigm and an expression paradigm) involving static facial stimuli. Table 6.1 provides an overview of the results of both studies. In this chapter, I describe how the results of the fMRI and EEG studies relate to one another and how the studies are different. Furthermore, I speculate about the role of several general ASD theories and/or mechanisms proposed to explain ASD-related face processing difficulties, and which face processing models are supported by our results. Finally, I describe several interesting questions for future research, and finalise this dissertation with a general conclusion.

1. Discussion

1.1. Similar behavioural performance on face processing tasks

We investigated facial expression processing at a behavioural level in both our fMRI and our EEG study, while facial identity processing was only behaviourally tested in the fMRI study. We used standardised behavioural face processing tasks, such as the Multimodal Emotion Recognition Test (MERT), Emotion Recognition Task (ERT) and Cambridge Face Memory Task (CFMT). These tasks were specifically selected to avoid a low-level perceptual matching strategy and included a memory component to increase the chances of observing group differences (Weigelt et al., 2012). Across studies, high functioning adults with ASD performed as well as age- and IQ-matched neurotypicals on a selection of face processing tasks, indicating a similar level of expertise in recognising facial identities and expressions. This is not in line with the general literature, as impaired performances on facial identity and expression tasks in individuals with ASD are often reported (Harms et al., 2010; Tang et al., 2015; Uljarevic & Hamilton, 2013; Weigelt et al., 2012). However, studies have also reported similar performances in both groups, although this typically results from studies in children (McPartland, Webb, et al., 2011; O'Hearn et al., 2010) or from using familiar faces as stimuli (Barton et al., 2004). For example, while children and adolescents with ASD seem unimpaired on the CFMT, adults with ASD showed a significant impairment (O'Hearn et al., 2010). This finding is interpreted as a disruption of the typical development of face processing in ASD. However, cohort effects cannot be ruled out, as adults might not have received equal support throughout development (Weigelt et al., 2012). Hence, our findings are not necessarily at odds with the literature but seem exceptional for the studied adult population. The adults that participated in our studies were recruited through psychiatric hospitals and received a formal diagnosis of ASD prior to participation, either as a child or in adulthood. Often, participants were diagnosed years ago, and received adequate support when required. We could speculate that this perhaps puts our ASD sample at an advantage compared to ASD samples from other studies, possibly explaining our finding that individuals with and without ASD performed similarly on a classical battery of standardised behavioural face processing tasks. In addition, it is also possible that we recruited exceptionally high functioning individuals with ASD, as ASD groups in both studies have IQ-scores well above average.

Table 6.1. Overview of results presented in Chapter 4 (fMRI) and Chapter 5 (EEG)

	Differences ASD-NT	No differences ASD-NT
fMRI study		
Behaviour	/	Same performance on standard face processing tasks and task during fMRI data acquisition
Univariate	/	Same levels of activation during face-processing
Multivariate	/	Same decoding accuracies in terms of facial identity and expression discrimination
Adaptation	/	Same release of adaptation to repeated facial identity, facial expression, and both
Functional connectivity	Hyperconnectivity in ASD: Amygdala – Inferior occipital Amygdala – V1	All other connections
EEG study		
Behaviour	/	Same performance on MERT (all modalities) and task during EEG data acquisition
Base rate	/	Same general neural synchronisation to faces
Oddball identity	/	Same neural sensitivity to different facial identities
Oddball expression	/	Same neural sensitivity to different facial expressions

1.2. Similar neural processing of facial identity and expression in ASD and NT groups

We investigated the neural processing of facial identities and expressions in high functioning adults with and without ASD. Across studies, face processing at a neural level was found to be very similar in both groups (Table 6.1). Results of our fMRI and our EEG study complement one another, showing different aspects of the neural processing of facial identity and expression. Furthermore, results are in line with one another, strengthening each other's conclusions. Our findings are not in line with the literature, as group differences at a neural level are often reported, across all approaches (Aoki et al., 2015; Di Martino et al., 2009; Dichter, 2012; Nomi & Uddin, 2015; Philip et al., 2012). These inconsistencies are likely due to the large variance in designs and approaches across reported studies, as well as the considerable heterogeneity of the ASD population (Vasa et al., 2016). ASD research in general has yielded many inconsistent findings, probably for the same reasons.

Neural activation levels in brain areas relevant for face processing were found to be similar in adults with and without ASD (Table 6.1), indicating brain areas were equally stimulated by the presentation of faces in both groups. We found a slightly higher response in V1 in neurotypicals, which did not survive correction for multiple comparisons. Nevertheless, this might suggest that neurotypicals paid slightly more attention to the faces (Gandhi et al., 1999; Moradi et al., 2012), which is in line with the proposed mechanism of reduced attention to faces driving atypical face processing in ASD (Chevallier et al., 2012; Schultz, 2005).

We observed no significant differences between individuals with and without ASD in terms of *neural decoding* of facial identities and expressions, indicating that facial identities and expressions are represented similarly in individuals with and without ASD. This is in line with another study using MVPA to investigate facial (expression) representations in ASD (Kliemann et al., 2018). For one region of interest, we found a close-to-significant uncorrected group difference. More specifically, the decoding accuracy of facial expressions is slightly higher in the anterior temporal cortex for individuals with ASD compared to neurotypicals. The decoding accuracy was not found to be significantly above chance in the ASD group, while it is clearly below chance level for neurotypicals. We can speculate that the anterior temporal cortex plays a small role in the processing of facial expressions in individuals with ASD, while it does not in neurotypicals.

Adaptation to facial identity and expression was not found to be significantly different between adults with and without ASD. Although the group differences did not reach significance, we observed that the amygdala and the anterior temporal cortex showed a release of adaptation to facial expressions in the ASD group but not the NT group. The finding in the anterior temporal cortex is in line with the trends found in our MVPA analyses, in which the decoding of expression was slightly higher in the anterior temporal cortex in the ASD group, again without reaching significance. We can speculate that the anterior temporal cortex, as well as the amygdala, seems somewhat more involved in the processing of facial expressions in individuals with ASD compared to neurotypicals, although statistical evidence cannot support this statement. Furthermore, in the FPVS-EEG identity paradigm, base stimuli were faces belonging to the same identity with changes only in size. Hence, base rate identity responses can be regarded as an index of neural adaptation to faces, comparable to the 'AllSame' condition in the fMRI study, which yielded similar results for individuals with and without ASD in both the fMRI and the EEG study.

No significant group differences were observed in terms of a *neural face inversion* effect, indicating that adults with ASD process faces holistically and similar to neurotypicals. This is in line with the general literature, in which an intact face inversion effect in ASD is often observed (Weigelt et al., 2012). As mentioned above, a developmental delay has been suggested, in which holistic processing of faces is thought to be intact in adults with ASD (Ventura et al., 2018). Based on our observation of an intact neural face inversion effect in ASD, we can carefully minimise the role of impaired holistic processing as a cause of face processing difficulties as suggested by the weak central coherence account (Happé & Frith, 2006), at least in high functioning adults with ASD. On the other hand, our findings do not contrast the enhanced perceptual functioning account, which suggests that - although individuals with ASD exhibit a superior low-level processing and local perceptual style - holistic processing is intact and can be used when it is needed (Mottron et al., 2006).

Neural sensitivity to detect expressions was found to be similar in both groups, indicating individuals with ASD are as sensitive as neurotypicals in discriminating expressive from neutral faces. These findings contrast with findings of robust differences between groups in studies using the same paradigm in children (Van der Donck et al., 2020). However, one expression shows a similar trend in adults: anger. Adult men with ASD, as boys with ASD, seem slightly less sensitive to discriminate angry faces rapidly and implicitly from neutral faces. Research has shown that children with ASD specifically avoid angry faces (García-Blanco et al., 2017) and avoid looking at the eyes of angry faces in particular (Wang et al.,

2018). In adults, authors have found a lack of so-called 'anger superiority' in ASD, an effect describing faster responses to angry faces than to other expressions, as anger is experienced as more threatening (Sasson et al., 2016). We can speculate that the slightly lower sensitivity to detect angry faces in adults with ASD might stem from a selective avoidance of angry faces throughout development, which resonates with both the active avoidance account (Kylliäinen & Hietanen, 2006; Richer, 1976) and the eye avoidance account (Tanaka & Sung, 2016), as well as the social motivation theory (Chevallier et al.,2012) as an explanation of face processing atypicalities to (angry) faces in individuals with ASD.

1.3. Significant differences between ASD and NT groups: functional connectivity

In the fMRI study, we found a slight difference in functional connectivity between individuals with and without ASD. More specifically, individuals with ASD showed a stronger functional connectivity between the amygdala and two low-level visual regions: the inferior occipital cortex (including the occipital face area OFA) and V1. This pattern of atypical connectivity has not yet been observed in previous research. Another study that investigated the connectivity between the amygdala and the occipital regions did not observe differences between adults with and without ASD (Murphy et al., 2012). This study instructed participants to judge expressions or age of presented faces, which is different from our instructions to look for differences between faces, although both studies used dynamic stimuli. In addition, the sample of Murphy and colleagues (2012) was half the size of our sample, had a higher standard deviation in age, and lower average IQ-scores, which could explain the difference in findings. In addition, the ASD population is highly heterogeneous, which could account for contrasting findings across studies.

In general (i.e., not specific to face processing), it has been suggested that a *generic underconnectivity* is at the root of difficulties experienced by individuals with ASD (Just et al., 2004; 2012). This is not in line with our findings, as we only find significant hyperconnectivity in ASD. However, non-significant hypoconnectivity in the ASD group was also observed. Another account of autism focuses on atypical amygdala activity in ASD (Baron-Cohen et al., 2000). This 'amygdala theory' includes atypicalities in activation of the amygdala and connections between the amygdala and other brain regions, but does not include statements about a connection between occipital regions and the amygdala.

Nonetheless, we can argue that atypical connections between occipital regions and the amygdala complement this theory.

The pattern of functional connectivity we observed may suggest that individuals with ASD attribute meaning to more basic perceptual features of faces, as the amygdala is involved in attributing salience and emotional valence to the perceptual input (Adolphs, 2010). In addition, this finding may resonate with basic physiological findings showing that faces are experienced as more arousing by individuals with ASD (Tanaka & Sung, 2016), and possibly also as more aversive or threatening (Robinson, 2007), which supports the active avoidance account as an explanation of face processing atypicalities in individuals with ASD (Kylliäinen & Hietanen, 2006; Richer, 1976). However, our study suggests that this initial over-reactivity does not seem to affect the further behavioural and neural processing of faces in terms of identity or expression. In addition, we can speculate that individuals with ASD assign a stronger meaning to more low-level facial features. In this light, our findings are not necessarily at odds with the literature, in which hypoconnectivity in ASD has been suggested mostly between high-level (and not low-level) brain regions involved in face processing (Abrams et al., 2013; Alaerts et al., 2013; Anderson et al., 2011; Guo et al., 2016; Kleinhans et al., 2008; Koshino et al., 2008). Possibly, the observed functional hyperconnectivity might have been formed in early life and remain present in adulthood, as children seem to process faces less holistically (i.e., with attention directed towards low-level facial features), which is in line with the weak central coherence account (Happé & Frith, 2006). This is also in line with a recent suggestion of an ASD-related developmental delay in holistic processing, in which fully intact holistic processing of faces is only reached by adulthood in ASD (Vettori, Dzhelyova, et al., 2019; Ventura et al., 2018).

1.4. Theories and mechanisms of ASD

Taking together the observed significant and non-significant differences between adults with and without ASD studied here, we cannot unequivocally resolve the question as to which mechanisms might play a role in the atypical face processing that is often observed in the ASD population. Note that proposed mechanisms are not mutually exclusive. For example, individuals with ASD can lack an inherent draw to faces, resulting in less attention towards the face, and still experience faces as aversive when they are forced to watch. First, we can speculate that our findings are mostly in line with the mechanism of reduced attention to faces in ASD (Schultz, 2005), the active avoidance account of atypical face

processing in ASD (Kylliäinen & Hietanen, 2006; Richer, 1976), and the *social motivation theory* (Chevallier et al., 2012). Faces seem inherently less salient for individuals with ASD, since we observed a lower average activation in the primary visual cortex while viewing faces. In addition, we found a slightly lower sensitivity to detect angry faces in ASD, and evidence of ASD-related atypical amygdala functioning during face processing, in terms of adaptation as well as functional connectivity, which might suggest that individuals with ASD experience faces in general, and angry faces in particular, as more arousing or even threatening than neurotypicals. Furthermore, we can speculate that our findings show evidence for a proposed developmental delay in the holistic processing of faces (Venture et al., 2018). Although we do not find an atypical face inversion effect, and thus do not find evidence to support the *weak central coherence account* of ASD (Happé & Frith, 2006), the observed atypical functional connectivity pattern might suggest that individuals with ASD attribute meaning to more low-level facial features, or that they did in early life, possibly indicating a local perceptual bias. This is in line with the *enhanced perceptual functioning* account (Mottron et al., 2006). Finally, we did not find support for the *predictive coding framework,* which hypothesizes that face processing is particularly difficult for individuals with ASD (Van de Cruys et al., 2014), such as a reduced face inversion effect or reduced adaptation. However, the difficulties are mostly thought to be true for naturalistic face processing, as standardized face processing tasks often do no entail as much 'noise' (e.g., hair removed, same viewpoint, same lighting conditions).

1.5. Differences between reported studies: design and participants

Using fMRI and EEG, we investigated facial identity and expression processing in adults with and without ASD. Results of these studies were highly consistent, as described above (see also Table 6.1). Interestingly, these consistent findings were attained using studies that were rather distinctive.

Firstly, although faces were presented in both studies, the *stimuli* were quite different. In the fMRI study, stimuli were dynamic faces, in which two faces belonging to the same identity were morphed from a neutral expression to a high intensity expressive face. In addition, facial identity and expression processing were investigated simultaneously, using a single paradigm. In contrast, stimuli were static in the EEG study, and facial identity and expression were investigated in separate sequences. In general, it has been suggested that dynamic facial stimuli yield stronger neural responses in social brain regions compared to

static facial stimuli (Kilts et al., 2003; LaBar et al., 2003; Sato et al., 2004; Trautmann et al., 2009). However, this enhanced response to dynamic stimuli was found to be lacking in individuals with ASD (Pelphrey et al., 2007; Sato et al., 2012). Due to this lack of enhancement to dynamic stimuli in ASD and the higher ecological validity of dynamic facial stimuli, it has been argued that dynamic stimuli might amplify the ASD-related neural atypicalities in face processing (Law Smith et al., 2010). Therefore, group differences were more likely to be observed in the fMRI study. We only observed one slight group difference in terms of functional connectivity.

Secondly, participants performed a different *task* while neuroimaging data was acquired. In the fMRI study, participants were instructed to observe the presented dynamic faces and react to any difference between one face and the next, regardless of whether this change occurred in identity or expression. Thus, participants were explicitly asked to focus on the presented faces. In addition, with a presentation time of two seconds, participants were able to consciously perceive the faces. A task with the focus on the presented faces, allowing for conscious facial processing, could have allowed for compensation at a perceptual level, possibly aiding individuals with ASD to mask atypicalities (Frank et al., 2018; Harms et al., 2010). In contrast, the task in the EEG study was completely orthogonal, asking participants to focus on the colour of a fixation cross instead of the presented faces. In addition, every static facial stimulus in the EEG study was presented for only around 167 ms, which does not allow for conscious perception (Rutiku et al., 2016). Hence, individuals with ASD were not able to use compensatory strategies in the FPVS-EEG approach. Results were similar in both studies, and we can conclude that individuals with ASD used little to no perceptual compensatory mechanisms to reach typical levels of facial identity and expression processing.

Finally, although *participants* were similar in both studies (i.e., only males participated in both studies, all participants with ASD received a formal diagnosis prior to participation), several important differences can be noted. The age of participants in the fMRI study was between 17 and 23 years, which is lower and less varied than participants in the EEG study, who were between 19 and 35 years old. In addition, the sample in the fMRI study had an average total IQ of 112, while the sample in the EEG study had an average total IQ of 107. Considering an average population IQ of 100 with a standard deviation of 15, both samples had an above-average IQ, with participants of the fMRI study being particularly high functioning. Hence, the sample that participated in the EEG study seems to be (slightly) more representative of the general (typical and ASD) population. However, a

limitation applicable to both studies is the fact that we cannot generalise our results to the ASD population as a whole, because our participants have average IQ-scores well above average. Finally, participants were sampled from roughly the same population in the same geographic region, which could cause a high overlap in participants between the studies. However, this was not the case: only two individuals with ASD participated in both studies, compared to one in the control group. Consistent findings in our fMRI and EEG study were thus attained in a distinct sample of a similar population, allowing some generalisation of our results.

1.6. Face processing models

1.6.1. Are facial identity and expression processing independent?

The dominant face processing framework of Haxby and colleagues (2000) suggests two separate neural routes for facial identity and facial expression processing. At a neural level, we studied facial identity and facial expression processing separately in the MVPA and adaptation analyses in the fMRI study, and we used two separate paradigms in the EEG study. Hence, it was possible to investigate these processes separately, and investigate the overlap between facial identity and facial expression results. We found that the processing of facial identity and expression are at least somewhat related, as results were similar for facial identity and facial expression processing. However, several small differences were observed.

Firstly, in the *superior temporal cortex*, facial expressions could be reliably distinguished based on neural representations, while this was not possible for facial identities. Indeed, research shows that this region is involved in the processing of dynamic facial expressions (Ishai et al., 2005). Recent studies have implicated the STS to process motion, and socially relevant motion in particular, including dynamic aspects of both facial identity and facial expressions (Campbell et al., 2001; Pitcher et al., 2014; Puce et al., 1998). In line with these studies, we observed a significant release from adaptation to both facial identity and expression in the superior temporal cortex. Altogether, this suggests that the superior temporal cortex is involved in both facial identity and facial expression processing, with a slightly larger involvement in facial expression processing.

Secondly, the *amygdala* was found to show significant release of adaptation to facial expressions but not identity, only in the ASD group. Indeed, the amygdala is widely known as the brain region involved in the processing of emotions (Adolphs, 2008). In contrast,

significant releases of adaptation to facial identity or expression were not observed in the NT group, and the group difference in terms of release of adaptation to facial expressions did not reach significance. Furthermore, patterns of amygdala activity were not informative to distinguish between facial identities or facial expressions in neither of the groups.

Thirdly, the *anterior temporal cortex* was found to show a significant release from adaptation to identity but not expression, only in the NT group. This indicates that it plays a role in the processing of facial identity but not facial expression. Indeed, the anterior temporal cortex has been suggested to be involved in the processing of facial identity, in particular familiar faces and semantic knowledge (Kriegeskorte & Bandettini, 2007; Nestor et al., 2011; Rotshtein et al., 2005; Sugiura et al., 2011). This is in line with the face processing model of Haxby and colleagues (2000), in which the anterior temporal cortex is part of the extended network as it aids the processing of facial identities by means of semantic knowledge (Gorno-Tempini et al., 1998). Nevertheless, the release from adaptation to both facial identity and facial expression was significant in the ASD group. In contrast, patterns of activity in the anterior temporal cortex were uninformative to distinguish between facial identities or facial expressions.

In sum, based on our fMRI findings, we would conclude that facial identity and facial expression processing are likely related, which is in line with previous research (Calder & Young, 2005; Xu & Biederman, 2010; Yankouskaya et al., 2017). We observed that the inferior occipital cortex (including the OFA), the posterior fusiform cortex (including the FFA) and the primary visual cortex process facial identity and facial expression very similarly. These findings are supported by our EEG study, as both paradigms yielded the same regions of interest, indicating that similar electrodes show the highest responses across all conditions (i.e., across inverted and upright faces, or across all four expressions). Additionally, the amygdala and the anterior temporal cortex also process facial identity and facial expression similarly, although slight differences can be observed. Only the superior temporal cortex showed informativeness for the processing of facial expressions while it did not for the processing of facial identities. Altogether, this suggests that facial identity and expression are likely related.

1.6.2. Which face processing model fits the results?

The most dominant face processing model was proposed by Haxby and colleagues (2000). We found the core brain regions proposed in this framework to be implicated in face

processing, and we observed that proposed core and extended face processing areas worked closely together as a face processing network. However, this dominant model suggests two separate neural routes for facial identity and facial expression processing. As mentioned above, this is not in line with our results, as we found the processing of facial identity and expression to be at least somewhat related. Additionally, Haxby and colleagues (2000) argued that the OFA is the sole entry point into the face processing network. However, brain lesion studies have shown that this is unlikely, as face processing abilities were found to be intact after damage to the OFA (Dalrymple et al., 2011; Sorger et al., 2007), and connectivity studies have shown connections between early visual areas and the OFA as well as the FFA (Gschwind et al., 2012; Pyles et al., 2013). Our results are in line with the latter, supporting the notion of multiple entry points into the face processing network, as we observed the strongest functional connections in the face processing network between V1 and the inferior occipital cortex (OFA), and between V1 and the posterior fusiform cortex (FFA).

Recently, a new neural framework for face processing was proposed by Duchaine and Yovel (2015). They suggest that neural routes are not separate in terms of identity or expression processing, but instead in terms of motion. In this new framework, the ventral stream processes form information (of both identity and expression), while the dorsal stream extracts motion information (of both identity and expression). Our functional connectivity findings support the suggestion of multiple pathways, with strong connections between the OFA and the FFA, but not between either of them and the STS, in line with previous research (Avidan et al., 2014; Gschwind et al., 2012; Pyles et al., 2013). Additionally, the proposed second pathway would include the superior temporal sulcus and the inferior frontal cortex (Duchaine & Yovel, 2015), which is in line with our functional connectivity results, as the superior temporal cortex is most strongly connected with inferior frontal regions. However, it is difficult to reach a conclusion as to the role of motion in both face processing streams based on our data. Nevertheless, we can conclude that our results do not contrast the proposed framework of Duchaine and Yovel (2015).

2. Future directions

We conducted an fMRI and an EEG study to investigate face processing in adult men with and without ASD. The paradigms used in our EEG study were the same as paradigms used in earlier studies in children (Van der Donck et al., 2020; Vettori, Dzhelyova, et al., 2019). Unexpectedly, we did not observe the same differences between adults with and without ASD, as our findings did not show significant differences between the groups. Therefore, it would be important to check whether the results from the FPVS-EEG studies in children can be replicated in the same population, and whether our findings can be replicated in adults. Very recently, our research group has been replicating the FPVS-EEG expression paradigm in children, and preliminary findings point to significant differences between children with and without ASD. Data from the identity paradigm have been acquired but not yet analysed. Moreover, this distinction in findings between children and adults inspires the question whether group differences would be observed when applying our fMRI paradigm in children, which is definitely an interesting avenue to explore in the future. I would expect to find differences between the groups when applying the fMRI paradigm in children with and without ASD, as was the case when the FPVS-EEG paradigm was applied in children. Importantly, these replications could provide information about a possible (neural) developmental delay in individuals with ASD, as we have found no differences between adults with and without ASD, while differences have been observed in children using the same paradigm.

In ASD research, participants have frequently been boys or men. This *male overrepresentation* has contributed to a vicious cycle causing women with ASD to not only be underrepresented in ASD research, but also underdiagnosed, as clinical criteria are based upon scientific findings (Happé & Frith, 2020). A probable reason is the idea that ASD predominantly affects males, and not females. Indeed, the number of boys to receive a diagnosis is higher than the number of girls. Often, the male-to-female ratio is suggested to be 4:1, meaning 1 girl is diagnosed for every 4 boys (Fombonne, 2020). However, a recent meta-analysis shows that this ratio is likely closer to 3:1, due to a diagnostic gender bias leaving girls at a higher risk of not receiving an ASD diagnosis when they do meet the clinical criteria (Loomes et al., 2017). Although autistic symptoms in females with ASD are often different from symptoms in males (Lai & Szatmari, 2020), both genders should be

represented in ASD studies. Both our fMRI and EEG paradigms can be used to study face processing in girls and women with ASD. Based on the little available literature, I would not expect to find differences between girls and women with ASD and age- and IQ-matched neurotypicals regarding face processing. Females with ASD likely acquire more visual experience as they have been found to pay more attention to social stimuli (such as faces) compared to males with ASD (Harrop et al., 2019). Indeed, one study observed that girls with a high risk of ASD show less difficulties with face processing than high-risk boys (Shephard et al., 2020). The overrepresentation of males in ASD research has recently started to change, with studies including both genders in their samples. This is a welcome evolution that should remain in place for future studies. In addition, studies should focus on girls and women with ASD, and investigate how symptoms, difficulties and neural mechanisms differ between sexes. In this way, the clinical practice can rely on scientific research to provide adequate care for both male and female individuals with ASD.

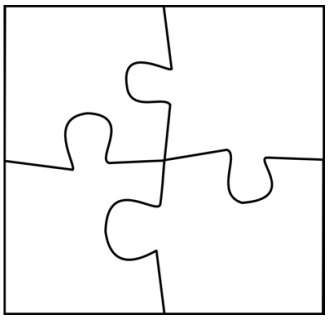
Not only males have been overrepresented in ASD research. In addition, research has often focused on relatively high functioning individuals with ASD, while largely ignoring *individuals at the lower end of the spectrum* that constitute approximately 55% of the ASD population (Charman et al., 2011; Russell et al., 2019). Sometimes, this is inherent to the method. For example, in the case of fMRI, it is essential that participants stay still throughout data-collection, often lasting over an hour. Experience has taught us that individuals on the lower end of the spectrum often cannot comply with these instructions. However, this is no reason to exclude this group from ASD research. New methods can be employed to include this group in studies, such as EEG combined with fast period visual stimulation (FVPS-EEG). In the future, our FPVS paradigm can be applied to investigate face processing in individuals at the lower end of the spectrum. I would hypothesise that differences in face processing between adults with and without ASD are more likely to show up in a sample of lower-functioning individuals, compared to our sample, as high functioning individuals with ASD are more likely to use compensating mechanisms to mask face processing difficulties. More possibilities to include lower-functioning individuals in neuroimaging research have been proposed in a review by Jack and Pelphrey (2017). With these new practices, the complete ASD spectrum can be studied, and scientific research can provide information to support clinical practice for individuals on the lower end of the spectrum as well.

A final note about future research concerns the current *COVID-19 pandemic*. As social beings, social distancing is taking its toll on our wellbeing. Mental health problems are

more prevalent, and likely long-lasting (O'Connor et al., 2021). The number and quality of real-life social interactions are severely diminished, as is the number of individuals to have interactions with. Furthermore, when the opportunity to socialise does arise, we often must cover the lower half of our face with a face mask. This does not necessarily disturb our ability to recognise someone, since the eyes are found to be more important than other facial features when processing facial identities (Royer et al., 2018; Sadr et al., 2003; Sekuler et al., 2004). In general, we also rely on the eye-region to recognise emotions. However, this is not true for one valuable emotion: happiness, for which we tend to focus on the mouth region (Grossmann, 2017; Smith et al., 2005). Furthermore, the mouth region contains necessary information to be able to distinguish expressions with similar 'eye-action', such as fear and surprise (Schyns et al., 2009). Face coverings can therefore make it more difficult to recognise how someone is feeling based on their facial expression. Individuals with ASD might be more severely affected. Especially children with ASD tend to rely on the mouth region a lot more for identity as well as expression processing compared to their neurotypical counterparts (Joseph & Tanaka, 2003; Tanaka et al., 2012; Tanaka & Sung, 2016; but see Vettori et al., 2020). Therefore, future research should keep in mind the possible repercussions of this pandemic, as only time will tell whether it will influence facial identity and emotion processing in young, developing individuals with and without socio-communicative disorders.

3. General conclusion

Humans are highly social beings. We are also social experts, as we can recognise who someone is and what that person is feeling in the blink of an eye. Research has often suggested that individuals with autism spectrum disorder experience difficulties with social interactions, and the processing of faces in particular. In our fMRI study, we found no evidence of these difficulties at a behavioural level and barely any evidence at a neural level, as reflected by the lack of differences between the groups. We only observed a small group difference in functional connectivity, with stronger connections between two low-level visual regions (V1 and the inferior occipital cortex) and the subcortical amygdala in the ASD group. This could indicate that individuals with ASD assign meaning to more low-level features of faces. Furthermore, our EEG analyses did not reveal any behavioural or neural differences between individuals with and without ASD. Notwithstanding the distinctiveness between the two studies, they yielded consistent results, therefore strengthening our conclusions. Altogether, we found little evidence of differences between high functioning adult men with and without ASD in terms of facial identity and expression processing.



References

Abrams, D. A., Lynch, C. J., Cheng, K. M., Phillips, J., Supekar, K., Ryali, S., Uddin, L. Q., & Menon, V. (2013). Underconnectivity between voice-selective cortex and reward circuitry in children with autism. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.1302982110

Adolphs, R. (2008). Fear, faces, and the human amygdala. In *Current Opinion in Neurobiology*. https://doi.org/10.1016/j.conb.2008.06.006

Adolphs, R. (2010). What does the amygdala contribute to social cognition? In *Annals of the New York Academy of Sciences*. https://doi.org/10.1111/j.1749-6632.2010.05445.x

Adolphs, R., Gosselin, F., Buchanan, T. W., Tranel, D., Schyns, P., & Damasio, A. R. (2005). A mechanism for impaired fear recognition after amygdala damage. *Nature*. https://doi.org/10.1038/nature03086

Adolphs, R., Sears, L., & Piven, J. (2001). Abnormal Processing of Social Information from Faces in Autism. *Journal of Cognitive Neuroscience*, *13*(2), 232–240. https://doi.org/10.1162/089892901564289

Adolphs, R., & Tranel, D. (1999). Intact recognition of emotional prosody following amygdala damage. *Neuropsychologia*. https://doi.org/10.1016/S0028-3932(99)00023-8

Adrian, E. D., & Matthews, B. H. C. (1934). The berger rhythm: Potential changes from the occipital lobes in man. *Brain*. https://doi.org/10.1093/brain/57.4.355

Aguirre, G. K. (2007). Continuous carry-over designs for fMRI. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2007.02.005

Alaerts, K., Woolley, D. G., Steyaert, J., Di Martino, A., Swinnen, S. P., & Wenderoth, N. (2013). Underconnectivity of the superior temporal sulcus predicts emotion recognition deficits in autism. *Social Cognitive and Affective Neuroscience*. https://doi.org/10.1093/scan/nst156

Alharbi, S. A., Button, K., Zhang, L., O'Shea, K. J., Fasolt, V., Lee, A. J., ... & Jones, B. C. (2020). Are affective factors related to individual differences in facial expression recognition?. *Royal Society open science*, *7*(9), 190699.

American Psychiatric Association. (1980). *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed.).

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders (5th ed.)*.

Anderson, J. S., Nielsen, J. A., Froehlich, A. L., Dubray, M. B., Druzgal, T. J., Cariello, A. N., Cooperrider, J. R., Zielinski, B. A., Ravichandran, C., Fletcher, P. T., Alexander, A. L., Bigler, E. D., Lange, N., & Lainhart, J. E. (2011). Functional connectivity magnetic resonance imaging classification of autism. *Brain*. https://doi.org/10.1093/brain/awr263

Andrews, T. J., & Ewbank, M. P. (2004). Distinct representations for facial identity and changeable aspects of faces in the human temporal lobe. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2004.07.060

Antshel, K. M., Zhang-James, Y., & Faraone, S. V. (2013). The comorbidity of ADHD and autism spectrum disorder. *Expert Review of Neurotherapeutics*, *13*(10), 1117–1128.

Antshel, K. M., Zhang-James, Y., Wagner, K. E., Ledesma, A., & Faraone, S. V. (2016). An update on the comorbidity of ADHD and ASD: a focus on clinical management. *Expert Review of Neurotherapeutics*, *16*(3), 279–293.

Anzellotti, S., Fairhall, S. L., & Caramazza, A. (2014). Decoding representations of face identity that are tolerant to rotation. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bht046

Apicella, F., Sicca, F., Federico, R. R., Campatelli, G., & Muratori, F. (2013). Fusiform gyrus responses to neutral and emotional faces in children with autism spectrum disorders: a high density ERP study. *Behavioural brain research*, *251*, 155-162.

Aoki, Y., Cortese, S., & Tansella, M. (2015). Neural bases of atypical emotional face processing in autism: A meta-analysis of fMRI studies. *World Journal of Biological Psychiatry*. https://doi.org/10.3109/15622975.2014.957719

Arsalidou, M., Morris, D., & Taylor, M. J. (2011). Converging evidence for the advantage of dynamic facial expressions. *Brain Topography*. https://doi.org/10.1007/s10548-011-0171-4

Ashwin, C., Baron-Cohen, S., Wheelwright, S., O'Riordan, M., & Bullmore, E. T. (2007). Differential activation of the amygdala and the 'social brain'during fearful face-processing in Asperger Syndrome. *Neuropsychologia*, *45*(1), 2-14.

Asperger, H. (1944). Die "Autistischen Psychopathen" im Kindesalter. *Archiv Für Psychiatrie Und Nervenkrankheiten*. https://doi.org/10.1007/BF01837709

Avidan, G., Tanzer, M., Hadj-Bouziane, F., Liu, N., Ungerleider, L. G., & Behrmann, M. (2014). Selective dissociation between core and extended regions of the face processing network in congenital prosopagnosia. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bht007

Axelrod, V., & Yovel, G. (2015). Successful decoding of famous faces in the fusiform face area. *PLoS ONE*. https://doi.org/10.1371/journal.pone.0117126

Bagby, R. M., Parker, J. D. A., & Taylor, G. J. (1994). The twenty-item Toronto Alexithymia Scale—I. Item selection and cross-validation of the factor structure. *Journal of Psychosomatic Research*, *38*(1), 23–32.

Balsters, J. H., Mantini, D., Apps, M. A. J., Eickhoff, S. B., & Wenderoth, N. (2016). Connectivity-based parcellation increases network detection sensitivity in resting state fMRI: An investigation into the cingulate cortex in autism. *NeuroImage: Clinical*. https://doi.org/10.1016/j.nicl.2016.03.016

Bänziger, T., Grandjean, D., & Scherer, K. R. (2009). Emotion recognition from expressions in face, voice, and body: the Multimodal Emotion Recognition Test (MERT). *Emotion*, *9*(5), 691.

Baria, A. T., Mansour, A., Huang, L., Baliki, M. N., Cecchi, G. A., Mesulam, M. M., & Apkarian, A. V. (2013). Linking human brain local activity fluctuations to structural and functional network architectures. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2013.01.072

Baron-Cohen, S., Leslie, A. M., & Frith, U. (1985). Does the autistic child have a "theory of mind" ? *Cognition* , *21* (1), 37–46. https://doi.org/10.1016/0010-0277(85)90022-8

Baron-Cohen, S., Ring, H. A., Bullmore, E. T., Wheelwright, S., Ashwin, C., & Williams, S. C. (2000). The amygdala theory of autism. *Neuroscience & Biobehavioral Reviews*, *24*(3), 355-364.

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The autism-spectrum quotient (AQ): Evidence from asperger syndrome/high functioning autism, malesand females, scientists and mathematicians. *Journal of Autism and Developmental Disorders*, *31*(1), 5–17.

Barton, J. J. S. (2008). Structure and function in acquired prosopagnosia: lessons from a series of 10 patients with brain damage. *Journal of Neuropsychology*, *2*(1), 197–225.

Barton, J. J. S., Cherkasova, M. V., Hefter, R., Cox, T. A., O'Connor, M., & Manoach, D. S. (2004). Are patients with social developmental disorders prosopagnosic? Perceptual heterogeneity in the Asperger and socio-emotional processing disorders. *Brain*, *127*(8), 1706–1716. https://doi.org/10.1093/brain/awh194

Barton, J. J. S., Press, D. Z., Keenan, J. P., & O'Connor, M. (2002). Lesions of the fusiform face area impair perception of facial configuration in prosopagnosia. *Neurology*, *58*(1), 71–78.

Batty, M., Meaux, E., Wittemeyer, K., Rogé, B., & Taylor, M. J. (2011). Early processing of emotional faces in children with autism: An event-related potential study. *Journal of Experimental Child Psychology*. https://doi.org/10.1016/j.jecp.2011.02.001

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). Manual for the Beck depression inventory-II. *San Antonio, TX: Psychological Corporation*.

Behrmann, M., Avidan, G., Leonard, G. L., Kimchi, R., Luna, B., Humphreys, K., & Minshew, N. (2006). Configural processing in autism and its relationship to face processing. *Neuropsychologia*, *44*(1), 110-129.

Benjamini, Y., & Hochberg, Y. (1995). Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society: Series B (Methodological)*. https://doi.org/10.1111/j.2517-6161.1995.tb02031.x

Bentin, S., Allison, T., Puce, A., Perez, E., & McCarthy, G. (1996). Electrophysiological studies of face perception in humans. *Journal of cognitive neuroscience*, *8*(6), 551-565.

Benton, A. L., Sivan, A. B., Hamsher, K. D. S., Varney, N., & Spreen, O. (1983). Facial Recognition: Stimulus and Multiple Choice Pictures. In *Contributions to neuropsychological assessment* (pp. 30–40). Oxford University Press.

Bernstein, M., & Yovel, G. (2015). Two neural pathways of face processing: A critical evaluation of current models. In *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2015.06.010

Bird, G., Catmur, C., Silani, G., Frith, C., & Frith, U. (2006). Attention does not modulate neural responses to

social stimuli in autism spectrum disorders. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2006.02.037

Birmingham, E., Cerf, M., & Adolphs, R. (2011). Comparing social attention in autism and amygdala lesions: Effects of stimulus and task condition. *Social Neuroscience*. https://doi.org/10.1080/17470919.2011.561547

Black, M. H., Chen, N. T. M., Iyer, K. K., Lipp, O. V., Bölte, S., Falkmer, M., Tan, T., & Girdler, S. (2017). Mechanisms of facial emotion recognition in autism spectrum disorders: Insights from eye tracking and electroencephalography. In *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2017.06.016

Bloch, C., Burghof, L., Lehnhardt, F.-G., Vogeley, K., & Falter-Wagner, C. (2021). Alexithymia traits outweigh autism traits in the explanation of depression in adults with autism. *Scientific Reports*, *11*(1), 1–7.

Boets, B., Op De Beeck, H. P., Vandermosten, M., Scott, S. K., Gillebert, C. R., Mantini, D., Bulthé, J., Sunaert, S., Wouters, J., & Ghesquière, P. (2013). Intact but less accessible phonetic representations in adults with dyslexia. *Science*. https://doi.org/10.1126/science.1244333

Brambati, S. M., Benoit, S., Monetta, L., Belleville, S., & Joubert, S. (2010). The role of the left anterior temporal lobe in the semantic processing of famous faces. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2010.06.045

Brewster, P. W. H., Mullin, C. R., Dobrin, R. A., & Steeves, J. K. E. (2011). Sex differences in face processing are mediated by handedness and sexual orientation. *Laterality*, *16*(2), 188–200.

Brothers, L. (1990). The neural basis of primate social communication. *Motivation and Emotion*. https://doi.org/10.1007/BF00991637

Bruce, V., & Young, A. (1986). Understanding face recognition. *British Journal of Psychology*, *77*, 305–327. https://doi.org/10.1111/j.2044-8295.1986.tb02199.x

Bulthé, J., De Smedt, B., & Op de Beeck, H. P. (2014). Format-dependent representations of symbolic and non-symbolic numbers in the human cortex as revealed by multi-voxel pattern analyses. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2013.10.049

Bulthé, J., De Smedt, B., & Op de Beeck, H. P. (2015). Visual number beats abstract numerical magnitude: Format-dependent representation of arabic digits and dot patterns in human parietal cortex. *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/jocn_a_00787

Bulthé, J., Prinsen, J., Vanderauwera, J., Duyck, S., Daniels, N., Gillebert, C. R., Mantini, D., Op de Beeck, H. P., & De Smedt, B. (2019). Multi-method brain imaging reveals impaired representations of number as well as altered connectivity in adults with dyscalculia. In *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2018.06.012

Busigny, T., Graf, M., Mayer, E., & Rossion, B. (2010). Acquired prosopagnosia as a face-specific disorder: Ruling out the general visual similarity account. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2010.03.026

Calder, A. J., & Young, A. W. (2005). Understanding the recognition of facial identity and facial expression. *Nature Reviews Neuroscience*, *6*(8), 641–651. https://doi.org/10.1038/nrn1724

Calvo, M. G., & Nummenmaa, L. (2008). Detection of emotional faces: salient physical features guide effective visual search. *Journal of Experimental Psychology: General*, *137*(3), 471.

Campbell, R., MacSweeney, M., Surguladze, S., Calvert, G., McGuire, P., Suckling, J., Brammer, M. J., & David, A. S. (2001). Cortical substrates for the perception of face actions: An fMRI study of the specificity of activation for seen speech and for meaningless lower-face acts (gurning). *Cognitive Brain Research*. https://doi.org/10.1016/S0926-6410(01)00054-4

Chang, C. C., & Lin, C. J. (2011). LIBSVM: A Library for support vector machines. *ACM Transactions on Intelligent Systems and Technology*. https://doi.org/10.1145/1961189.1961199

Charman, T., Jones, C. R. G., Pickles, A., Simonoff, E., Baird, G., & Happé, F. (2011). Defining the cognitive phenotype of autism. *Brain Research*, *1380*, 10–21.

Chevallier, C., Kohls, G., Troiani, V., Brodkin, E. S., & Schultz, R. T. (2012). The social motivation theory of autism. *Trends in Cognitive Sciences*, *16*(4), 231–239.

Chiarotti, F., & Venerosi, A. (2020). Epidemiology of autism spectrum disorders: A review of worldwide prevalence estimates since 2014. In *Brain Sciences*. https://doi.org/10.3390/brainsci10050274

Christensen, J., Grnøborg, T. K., Srøensen, M. J., Schendel, D., Parner, E. T., Pedersen, L. H., & Vestergaard, M.

(2013). Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA - Journal of the American Medical Association*. https://doi.org/10.1001/jama.2013.2270

Cohen Kadosh, K., Henson, R. N. A., Cohen Kadosh, R., Johnson, M. H., & Dick, F. (2010). Task-dependent activation of face-sensitive cortex: An fMRI adaptation study. *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/jocn.2009.21224

Constantino, J. N., & Todd, R. D. (2005). Intergenerational transmission of subthreshold autistic traits in the general population. *Biological Psychiatry*. https://doi.org/10.1016/j.biopsych.2004.12.014

Cook, R., Shah, P., Gaule, A., Brewer, R., & Bird, G. (2015). Autism and developmental prosopagnosia: A cross-disorder study. *Journal of Vision*, *15*(12), 1211.

Corrow, S. L., Dalrymple, K. A., & Barton, J. J. S. (2016). Prosopagnosia: current perspectives. *Eye and Brain*, *8*, 165.

Critchley, H. D., Daly, E. M., Bullmore, E. T., Williams, S. C. R., Van Amelsvoort, T., Robertson, D. M., Rowe, A., Phillips, M., McAlonan, G., Howlin, P., & Murphy, D. G. M. (2000). The functional neuroanatomy of social behaviour: Changes in cerebral blood flow when people with autistic disorder process facial expressions. *Brain*, *123*(11), 2203–2212. https://doi.org/10.1093/brain/123.11.2203

Croen, L. A., Zerbo, O., Qian, Y., Massolo, M. L., Rich, S., Sidney, S., & Kripke, C. (2015). The health status of adults on the autism spectrum. *Autism*, *19*(7), 814–823.

Cygan, H. B., Okuniewska, H., Jednoróg, K., Marchewka, A., Wypych, M., & Nowicka, A. (2018). Face processing in a case of high functioning autism with developmental prosopagnosia. *Acta Neurobiol Exp*, *78*, 114–131.

Dalrymple, K. A., Oruç, I., Duchaine, B., Pancaroglu, R., Fox, C. J., Iaria, G., Handy, T. C., & Barton, J. J. S. (2011). The anatomic basis of the right face-selective N170 IN acquired prosopagnosia: A combined ERP/fMRI study. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2011.05.003

Dawson, G., Webb, S. J., & McPartland, J. (2005). Understanding the Nature of Face Processing Impairment in Autism: Insights From Behavioral and Electrophysiological Studies. *Developmental Neuropsychology*, *27*(3), 403–424. https://doi.org/10.1207/s15326942dn2703_6

De Jong, M.C., Van Engeland, H., Kemner, C. (2008). Attentional Effects of Gaze Shifts Are Influenced by Emotion and Spatial Frequency, but Not in Autism. *Journal of American Academy of Child and Adolescent Psychiatry 47*(4), 443- 454.

De Renzi, E., Faglioni, P., Grossi, D., & Nichelli, P. (1991). Apperceptive and associative forms of prosopagnosia. *Cortex*, *27*(2), 213–221.

Destefano, F., Bodenstab, H. M., & Offit, P. A. (2019). Principal Controversies in Vaccine Safety in the United States. *Clinical Infectious Diseases*. https://doi.org/10.1093/cid/ciz135

Di Martino, A., O'Connor, D., Chen, B., Alaerts, K., Anderson, J. S., Assaf, M., Balsters, J. H., Baxter, L., Beggiato, A., Bernaerts, S., Blanken, L. M. E., Bookheimer, S. Y., Braden, B. B., Byrge, L., Castellanos, F. X., Dapretto, M., Delorme, R., Fair, D. A., Fishman, I., … Milham, M. P. (2017). Enhancing studies of the connectome in autism using the autism brain imaging data exchange II. *Scientific Data*. https://doi.org/10.1038/sdata.2017.10

Di Martino, A., Ross, K., Uddin, L. Q., Sklar, A. B., Castellanos, F. X., & Milham, M. P. (2009). Functional Brain Correlates of Social and Nonsocial Processes in Autism Spectrum Disorders: An Activation Likelihood Estimation Meta-Analysis. *Biological Psychiatry*. https://doi.org/10.1016/j.biopsych.2008.09.022

Di Martino, A., Yan, C. G., Li, Q., Denio, E., Castellanos, F. X., Alaerts, K., Anderson, J. S., Assaf, M., Bookheimer, S. Y., Dapretto, M., Deen, B., Delmonte, S., Dinstein, I., Ertl-Wagner, B., Fair, D. A., Gallagher, L., Kennedy, D. P., Keown, C. L., Keysers, C., … Milham, M. P. (2014). The autism brain imaging data exchange: Towards a large-scale evaluation of the intrinsic brain architecture in autism. *Molecular Psychiatry*. https://doi.org/10.1038/mp.2013.78

Dichter, G. S. (2012). Functional magnetic resonance imaging of autism spectrum disorders. *Dialogues in Clinical Neuroscience*, *14*(3), 319–351.

Dobs, K., Schultz, J., Bülthoff, I., & Gardner, J. L. (2018). Task-dependent enhancement of facial expression and identity representations in human cortex. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2018.02.013

Domes, G., Heinrichs, M., Kumbier, E., Grossmann, A., Hauenstein, K., & Herpertz, S. C. (2013). Effects of intranasal oxytocin on the neural basis of face processing in autism spectrum disorder. *Biological Psychiatry*. https://doi.org/10.1016/j.biopsych.2013.02.007

Drucker, D. M., & Aguirre, G. K. (2009). Different spatial scales of shape similarity representation in lateral and ventral LOC. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhn244

Duchaine, B, & Nakayama, K. (2006). Developmental prosopagnosia: a window to content-specific face processing. In *Current Opinion in Neurobiology*. https://doi.org/10.1016/j.conb.2006.03.003

Duchaine, B, & Yovel, G. (2015). A Revised Neural Framework for Face Processing. *Annual Review of Vision Science*. https://doi.org/10.1146/annurev-vision-082114-035518

Duchaine, Brad, & Nakayama, K. (2006). The Cambridge Face Memory Test: Results for neurologically intact individuals and an investigation of its validity using inverted face stimuli and prosopagnosic participants. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2005.07.001

Dwyer, P., Xu, B., & Tanaka, J. W. (2019). Investigating the perception of face identity in adults on the autism spectrum using behavioural and electrophysiological measures. *Vision Research*. https://doi.org/10.1016/j.visres.2018.02.013

Dzhelyova, M., Jacques, C., & Rossion, B. (2017). At a single glance: Fast periodic visual stimulation uncovers the spatio-temporal dynamics of brief facial expression changes in the human brain. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhw223

Dzhelyova, M., & Rossion, B. (2014a). Supra-additive contribution of shape and surface information to individual face discrimination as revealed by fast periodic visual stimulation. *Journal of Vision*, *14*(14), 15.

Dzhelyova, M., & Rossion, B. (2014b). The effect of parametric stimulus size variation on individual face discrimination indexed by fast periodic visual stimulation. *BMC Neuroscience*, *15*(1), 1–12.

Ebisch, S. J. H., Mantini, D., Romanelli, R., Tommasi, M., Perrucci, M. G., Romani, G. L., Colom, R., & Saggino, A. (2013). Long-range functional interactions of anterior insula and medial frontal cortex are differently modulated by visuospatial and inductive reasoning tasks. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2013.04.058

Ekman, P., & Cordaro, D. (2011). What is meant by calling emotions basic. *Emotion Review*. https://doi.org/10.1177/1754073911410740

Elsabbagh, M., Divan, G., Koh, Y. J., Kim, Y. S., Kauchali, S., Marcín, C., Montiel-Nava, C., Patel, V., Paula, C. S., Wang, C., Yasamy, M. T., & Fombonne, E. (2012). Global Prevalence of Autism and Other Pervasive Developmental Disorders. *Autism Research*. https://doi.org/10.1002/aur.239

Engell, A. D., & McCarthy, G. (2013). Probabilistic atlases for face and biological motion perception: An analysis of their reliability and overlap. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2013.02.025

Evers, K., Steyaert, J., Noens, I., & Wagemans, J. (2015). Reduced Recognition of Dynamic Facial Emotional Expressions and Emotion-Specific Response Bias in Children with an Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-014-2337-x

Ewbank, M. P., Pell, P. J., Powell, T. E., Von Dem Hagen, E. A. H., Baron-Cohen, S., & Calder, A. J. (2017). Repetition suppression and memory for faces is reduced in adults with autism spectrum conditions. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhw373

Fair, D. A., Schlaggar, B. L., Cohen, A. L., Miezin, F. M., Dosenbach, N. U. F., Wenger, K. K., Fox, M. D., Snyder, A. Z., Raichle, M. E., & Petersen, S. E. (2007). A method for using blocked and event-related fMRI data to study "resting state" functional connectivity. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2006.11.051

Faja, S., Dawson, G., Aylward, E., Wijsman, E. M., & Webb, S. J. (2016). Early event-related potentials to emotional faces differ for adults with autism spectrum disorder and by serotonin transporter genotype. *Clinical Neurophysiology*. https://doi.org/10.1016/j.clinph.2016.02.022

Falck-Ytter, T., & von Hofsten, C. (2011). How special is social looking in ASD: a review. *Progress in Brain Research*, *189*, 209–222.

Feuerriegel, D., Churches, O., Hofmann, J., & Keage, H. A. D. (2015). The N170 and face perception in psychiatric and neurological disorders: A systematic review. *Clinical Neurophysiology*, *126*(6), 1141–1158.

Fietz, J., Valencia, N., & Silani, G. (2018). Alexithymia and autistic traits as possible predictors for traits related to depression, anxiety, and stress: A multivariate statistical approach. *Journal of Evaluation in Clinical Practice*, *24*(4), 901–908.

Fombonne, E. (2020). Epidemiological controversies in autism. In *Swiss Archives of Neurology, Psychiatry and Psychotherapy*. https://doi.org/10.4414/sanp.2020.03084

Fox, C. J., Hanif, H. M., Iaria, G., Duchaine, B. C., & Barton, J. J. S. (2011). Perceptual and anatomic patterns of

selective deficits in facial identity and expression processing. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2011.07.018

Fox, C. J., Iaria, G., & Barton, J. J. S. (2009). Defining the face processing network: Optimization of the functional localizer in fMRI. *Human Brain Mapping*. https://doi.org/10.1002/hbm.20630

Fox, C. J., Moon, S. Y., Iaria, G., & Barton, J. J. S. (2009). The correlates of subjective perception of identity and expression in the face network: An fMRI adaptation study. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2008.09.011

Frank, R., Schulze, L., Hellweg, R., Koehne, S., & Roepke, S. (2018). Impaired detection and differentiation of briefly presented facial emotions in adults with high functioning autism and Asperger syndrome. *Behaviour Research and Therapy*, *104*, 7–13.

Franz, M., Popp, K., Schaefer, R., Sitte, W., Schneider, C., Hardt, J., Decker, O., & Braehler, E. (2008). Alexithymia in the German general population. *Social Psychiatry and Psychiatric Epidemiology*, *43*(1), 54–62.

Frässle, S., Krach, S., Paulus, F. M., & Jansen, A. (2016). Handedness is related to neural mechanisms underlying hemispheric lateralization of face processing. *Scientific Reports*, *6*(1), 1–17.

Furl, N., Henson, R. N., Friston, K. J., & Calder, A. J. (2013). Top-down control of visual responses to fear by the amygdala. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.2992-13.2013

Furl, N., Henson, R. N., Friston, K. J., & Calder, A. J. (2015). Network interactions explain sensitivity to dynamic faces in the superior temporal sulcus. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhu083

Fusar-poli, P., Placentino, A., Carletti, F., Landi, P., Allen, P., Surguladze, S., Benedetti, F., Abbamonte, M., Gasparotti, R., Barale, F., Perez, J., Mcguire, P., & Politi, P. (2009). *Functional atlas of emotional faces processing : a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies*. *44*(0), 418–432.

Gainotti, G. (2019). Emotions and the right hemisphere: can new data clarify old models? *The Neuroscientist*, *25*(3), 258–270.

Gandhi, S. P., Heeger, D. J., & Boynton, G. M. (1999). Spatial attention affects brain activity in human primary visual cortex. *Proceedings of the National Academy of Sciences*, *96*(6), 3314–3319.

Gao, X., & Maurer, D. (2009). Influence of intensity on children's sensitivity to happy, sad, and fearful facial expressions. *Journal of Experimental Child Psychology*, *102*(4), 503–521.

García-Blanco, A., López-Soler, C., Vento, M., García-Blanco, M. C., Gago, B., & Perea, M. (2017). Communication deficits and avoidance of angry faces in children with autism spectrum disorder. *Research in Developmental Disabilities*, *62*, 218–226.

Gilbert, S. J., Meuwese, J. D. I., Towgood, K. J., Frith, C. D., & Burgess, P. W. (2009). Abnormal functional specialization within medial prefrontal cortex in high functioning autism: A multi-voxel similarity analysis. *Brain*. https://doi.org/10.1093/brain/awn365

Gillebert, C. R., & Mantini, D. (2013). Functional connectivity in the normal and injured brain. In *Neuroscientist*. https://doi.org/10.1177/1073858412463168

Goesaert, E., & Op de Beeck, H. P. (2013). Representations of facial identity information in the ventral visual stream investigated with multivoxel pattern analyses. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.1829-12.2013

Gorno-Tempini, M. L., Price, C. J., Josephs, O., Vandenberghe, R., Cappa, S. F., Kapur, N., Frackowiak, R. S., & Tempini, M. L. (1998). The neural systems sustaining face and proper-name processing. *Brain*, *121*(11), 2103–2118.

Griffiths, S., Jarrold, C., Penton-Voak, I. S., Woods, A. T., Skinner, A. L., & Munafò, M. R. (2019). Impaired recognition of basic emotions from facial expressions in young people with autism spectrum disorder: Assessing the importance of expression intensity. *Journal of Autism and Developmental Disorders*, *49*(7), 2768–2778.

Grill-spector, K., Knouf, N., & Kanwisher, N. (2004). The fusiform face area subserves face perception, not generic within-category identification. *Nature Neuroscience*, *7*(5), 555–562. https://doi.org/10.1038/nn1224

Grossman, E. D., Battelli, L., & Pascual-Leone, A. (2005). Repetitive TMS over posterior STS disrupts perception of biological motion. *Vision Research*. https://doi.org/10.1016/j.visres.2005.05.027

Grossman, E., Donnelly, M., Price, R., Pickens, D., Morgan, V., Neighbor, G., & Blake, R. (2000). Brain areas involved in perception of biological motion. *Journal of Cognitive Neuroscience*.

https://doi.org/10.1162/089892900562417

Grossmann, T. (2017). The Eyes as Windows Into Other Minds: An Integrative Perspective. In *Perspectives on Psychological Science*. https://doi.org/10.1177/1745691616654457

Grynberg, D., Chang, B., Corneille, O., Maurage, P., Vermeulen, N., Berthoz, S., & Luminet, O. (2012). Alexithymia and the processing of emotional facial expressions (EFEs): systematic review, unanswered questions and further perspectives. *PloS One*, *7*(8), e42429.

Gschwind, M., Pourtois, G., Schwartz, S., Van De Ville, D., & Vuilleumier, P. (2012). White-matter connectivity between face-responsive regions in the human brain. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhr226

Guex, R., Méndez-Bértolo, C., Moratti, S., Strange, B. A., Spinelli, L., Murray, R. J., Sander, D., Seeck, M., Vuilleumier, P., & Domínguez-Borràs, J. (2020). Temporal dynamics of amygdala response to emotion- and action-relevance. *Scientific Reports*. https://doi.org/10.1038/s41598-020-67862-1

Guillon, Q., Hadjikhani, N., Baduel, S., & Rogé, B. (2014). Visual social attention in autism spectrum disorder: Insights from eye tracking studies. *Neuroscience & Biobehavioral Reviews*, *42*, 279–297.

Guo, X., Duan, X., Long, Z., Chen, H., Wang, Y., Zheng, J., Zhang, Y., Li, R., & Chen, H. (2016). Decreased amygdala functional connectivity in adolescents with autism: A resting-state fMRI study. *Psychiatry Research - Neuroimaging*. https://doi.org/10.1016/j.pscychresns.2016.10.005

Hadjikhani, N., Chabris, C. F. A. C. F., Joseph, R. M., Clark, J., McGrath, L., Aharon, I., Feczko, E., Tager-Flusberg, H., & Harris, G. J. (2004). Early visual cortex organization in autism: An fMRI study. *NeuroReport*, *15*(2). https://doi.org/10.1097/00001756-200402090-00011

Hadjikhani, N., Joseph, R., Snyder, J., Chabris, C. F., Clark, J., Steele, S., McGrath, L., Vangel, M., Aharon, I., Feczko, E., Harris, G. J., & Tager-Flusberg, H. (2004). Activation of the fusiform gyrus when individuals with autism spectrum disorder view faces. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2004.03.025

Hahamy, A., Behrmann, M., & Malach, R. (2015). The idiosyncratic brain: Distortion of spontaneous connectivity patterns in autism spectrum disorder. *Nature Neuroscience*. https://doi.org/10.1038/nn.3919

Happé, F. (2003). Theory of mind and the self. *Annals of the New York Academy of Sciences*, *1001*(1), 134-144.

Happé, F., & Frith, U. (2006). The weak coherence account: Detail-focused cognitive style in autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *36*(1), 5–25. doi:10.1007/s10803-005-0039-0

Happé, F., & Frith, U. (2020). Annual Research Review: Looking back to look forward–changes in the concept of autism and implications for future research. *Journal of Child Psychology and Psychiatry*, *61*(3), 218–232.

Harms, M. B., Martin, A., & Wallace, G. L. (2010). Facial emotion recognition in autism spectrum disorders: A review of behavioral and neuroimaging studies. *Neuropsychology Review*, *20*(3), 290–322. https://doi.org/10.1007/s11065-010-9138-6

Harris, R. J., Young, A. W., & Andrews, T. J. (2014). Dynamic stimuli demonstrate a categorical representation of facial expression in the amygdala. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2014.01.005

Harrop, C., Jones, D., Zheng, S., Nowell, S., Schultz, R., & Parish-Morris, J. (2019). Visual attention to faces in children with autism spectrum disorder: are there sex differences?. *Molecular Autism*, *10*(1), 1-10.

Harry, B., Williams, M. A., Davis, C., & Kim, J. (2013). Emotional expressions evoke a differential response in the fusiform face area. *Frontiers in Human Neuroscience*. https://doi.org/10.3389/fnhum.2013.00692

Haxby, J. V., Hoffman, E. A., & Gobbini, M. I. (2000). The distributed human neural system for face perception. *Trends in Cognitive Sciences*, *4*(6), 223–233. https://doi.org/10.1016/S1364-6613(00)01482-0

Haxby, J. V., Hoffman, E. A., & Gobbini, M. I. (2002). Human neural systems for face recognition and social communication. In *Biological Psychiatry*. https://doi.org/10.1016/S0006-3223(01)01330-0

Haxby, J. V., Petit, L., Ungerleider, L. G., & Courtney, S. M. (2000). Distinguishing the functional roles of multiple regions in distributed neural systems for visual working memory. *NeuroImage*. https://doi.org/10.1006/nimg.2000.0592

Haxby, J. V, Gobbini, M. I., Furey, M. L., Ishai, A., Schouten, J. L., & Pietrini, P. (2001). Distributed and overlapping representations of faces and objects in ventral temporal cortex. *Science*, *293*(September), 2425–2430. https://doi.org/10.1126/science.1063736

Haynes, J. D., & Rees, G. (2006). Decoding mental states from brain activity in humans. In *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn1931

Hedley, D., Brewer, N., & Young, R. (2015). The Effect of Inversion on Face Recognition in Adults with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-014-2297-1

Hendriks, M. H. A., Dillen, C., Vettori, S., Vercammen, L., Daniels, N., Steyaert, J., de Beeck, H. O., & Boets, B. (2021). Neural processing of facial identity and expression in adults with and without autism: A multi-method approach. *NeuroImage: Clinical*, *29*, 102520.

Hileman, C. M., Henderson, H., Mundy, P., Newell, L., & Jaime, M. (2011). Developmental and individual differences on the P1 and N170 ERP components in children with and without autism. *Developmental Neuropsychology*. https://doi.org/10.1080/87565641.2010.549870

Hinojosa, J. A., Mercado, F., & Carretié, L. (2015). N170 sensitivity to facial expression: A meta-analysis. *Neuroscience & Biobehavioral Reviews*, *55*, 498–509.

Hoekstra, R. A., Bartels, M., Cath, D. C., & Boomsma, D. I. (2008). Factor structure, reliability and criterion validity of the Autism-Spectrum Quotient (AQ): a study in Dutch population and patient groups. *Journal of Autism and Developmental Disorders*, *38*(8), 1555–1566.

Hoffman, E. A., & Haxby, J. V. (2000). Distinct representations of eye gaze and identity in the distributed human neural system for face perception. *Nature Neuroscience*. https://doi.org/10.1038/71152

Holland, C. A. C., Ebner, N. C., Lin, T., & Samanez-Larkin, G. R. (2019). Emotion identification across adulthood using the Dynamic FACES database of emotional expressions in younger, middle aged, and older adults. *Cognition and Emotion*, *33*(2), 245–257.

Hubl, D., Bölte, S., Feineis–Matthews, S., Lanfermann, H., Federspiel, A., Strik, W., ... & Dierks, T. (2003). Functional imbalance of visual pathways indicates alternative face processing strategies in autism. *Neurology*, *61*(9), 1232-1237.

Hull, J. V., Jacokes, Z. J., Torgerson, C. M., Irimia, A., Van Horn, J. D., Aylward, E., Bernier, R., Bookheimer, S., Dapretto, M., Gaab, N., Geschwind, D., Jack, A., Nelson, C., Pelphrey, K., State, M., Ventola, P., & Webb, S. J. (2017). Resting-state functional connectivity in autism spectrum disorders: A review. In *Frontiers in Psychiatry*. https://doi.org/10.3389/fpsyt.2016.00205

Hultman, C. M., Sandin, S., Levine, S. Z., Lichtenstein, P., & Reichenberg, A. (2011). Advancing paternal age and risk of autism: New evidence from a population-based study and a meta-analysis of epidemiological studies. *Molecular Psychiatry*. https://doi.org/10.1038/mp.2010.121

Humphreys, K., Hasson, U., Avidan, G., Minshew, N., & Behrmann, M. (2008). Cortical patterns of category-Selective activation for faces, places and objects in adults with autism. *Autism Research*. https://doi.org/10.1002/aur.1

Ishai, A. (2008). Let's face it: It's a cortical network. *NeuroImage*, *40*(2), 415–419. https://doi.org/10.1016/j.neuroimage.2007.10.040

Ishai, A., Schmidt, C. F., & Boesiger, P. (2005). *Face perception is mediated by a distributed cortical network*. *67*, 87–93. https://doi.org/10.1016/j.brainresbull.2005.05.027

Jack, A., & A. Pelphrey, K. (2017). Annual Research Review: Understudied populations within the autism spectrum–current trends and future directions in neuroimaging research. *Journal of Child Psychology and Psychiatry, 58*(4), 411-435.

Jamal, W., Cardinaux, A., Haskins, A. J., Kjelgaard, M., & Sinha, P. (2020). Reduced Sensory Habituation in Autism and Its Correlation with Behavioral Measures. *Journal of Autism and Developmental Disorders*, 1-12.

Jeste, S. S., & Nelson, C. A. (2009). Event related potentials in the understanding of autism spectrum disorders: an analytical review. *Journal of Autism and Developmental Disorders*, *39*(3), 495–510.

Johnson, M. H., Dziurawiec, S., Ellis, H., & Morton, J. (1991). Newborns' preferential tracking of face-like stimuli and its subsequent decline. *Cognition*, *40*(1–2), 1–19.

Johnson, M. H., Senju, A., & Tomalski, P. (2015). The two-process theory of face processing: modifications based on two decades of data from infants and adults. *Neuroscience & Biobehavioral Reviews*, *50*, 169–179.

Jonas, J., Jacques, C., Liu-Shuang, J., Brissart, H., Colnat-Coulbois, S., Maillard, L., & Rossion, B. (2016). A face-selective ventral occipito-temporal map of the human brain with intracerebral potentials. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.1522033113

Jørgensen, M. M., Zachariae, R., Skytthe, A., & Kyvik, K. (2007). Genetic and environmental factors in alexithymia: a population-based study of 8,785 Danish twin pairs. *Psychotherapy and Psychosomatics*, *76*(6), 369–375.

Joseph, R. M., & Tanaka, J. (2003). Holistic and part-based face recognition in children with autism. *Journal of Child Psychology and Psychiatry*, *44*(4), 529–542.

Joshi, G., Wozniak, J., Petty, C., Martelon, M. K., Fried, R., Bolfek, A., Kotte, A., Stevens, J., Furtak, S. L., & Bourgeois, M. (2013). Psychiatric comorbidity and functioning in a clinically referred population of adults with autism spectrum disorders: a comparative study. *Journal of Autism and Developmental Disorders*, *43*(6), 1314–1325.

Julian, J. B., Fedorenko, E., Webster, J., & Kanwisher, N. (2012). An algorithmic method for functionally defining regions of interest in the ventral visual pathway. *NeuroImage*, *60*(4), 2357–2364. https://doi.org/10.1016/j.neuroimage.2012.02.055

Just, M. A., Cherkassky, V. L., Keller, T. A., & Minshew, N. J. (2004). Cortical activation and synchronization during sentence comprehension in high functioning autism: evidence of underconnectivity. *Brain*, *127*(8), 1811-1821.

Just, M. A., Keller, T. A., Malave, V. L., Kana, R. K., & Varma, S. (2012). Autism as a neural systems disorder: a theory of frontal-posterior underconnectivity. *Neuroscience & Biobehavioral Reviews*, *36*(4), 1292-1313.

Kang, E., Keifer, C. M., Levy, E. J., Foss-Feig, J. H., McPartland, J. C., & Lerner, M. D. (2018). Atypicality of the N170 Event-Related Potential in Autism Spectrum Disorder: A Meta-analysis. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. https://doi.org/10.1016/j.bpsc.2017.11.003

Kanner, L. (1943). Autistic disturbances of affective contact. *Nervous Child*, *2*(3), 217-250.

Kanwisher, N., & Barton, J. J. S. (2011). The functional architecture of the face system: Integrating evidence from fMRI and patient studies. *The Oxford Handbook of Face Perception*, 111–129.

Kanwisher, N., McDermott, J., & Chun, M. M. (1997). The fusiform face area: A module in human extrastriate cortex specialized for face perception. *Journal of Neuroscience*. https://doi.org/10.1523/jneurosci.17-11-04302.1997

Kanwisher, N., & Yovel, G. (2006). The fusiform face area: A cortical region specialized for the perception of faces. In *Philosophical Transactions of the Royal Society B: Biological Sciences*. https://doi.org/10.1098/rstb.2006.1934

Kemp, A. H., & Guastella, A. J. (2011). The role of oxytocin in human affect: A novel hypothesis. In *Current Directions in Psychological Science*. https://doi.org/10.1177/0963721411417547

Kennerknecht, I., Pluempe, N., Edwards, S., & Raman, R. (2007). Hereditary prosopagnosia (HPA): the first report outside the Caucasian population. *Journal of Human Genetics*, *52*(3), 230–236.

Kennerknecht, I., Pluempe, N., & Welling, B. (2008). Congenital prosopagnosia–a common hereditary cognitive dysfunction in humans. *Frontiers in Bioscience*, *13*(1), 3150–3158.

Keown, C. L., Shih, P., Nair, A., Peterson, N., Mulvey, M. E., & Müller, R. A. (2013). Local functional overconnectivity in posterior brain regions is associated with symptom severity in autism spectrum disorders. *Cell Reports*. https://doi.org/10.1016/j.celrep.2013.10.003

Kessels, R. P. C., Montagne, B., Hendriks, A. W., Perrett, D. I., & De Haan, E. H. F. (2014). Assessment of perception of morphed facial expressions using the Emotion Recognition Task: Normative data from healthy participants aged 8-75. *Journal of Neuropsychology*. https://doi.org/10.1111/jnp.12009

Kilts, C. D., Egan, G., Gideon, D. A., Ely, T. D., & Hoffman, J. M. (2003). Dissociable neural pathways are involved in the recognition of emotion in static and dynamic facial expressions. *NeuroImage*. https://doi.org/10.1006/nimg.2002.1323

Kim, Y. S., Fombonne, E., Koh, Y. J., Kim, S. J., Cheon, K. A., & Leventhal, B. L. (2014). A comparison of DSM-IV pervasive developmental disorder and DSM-5 autism spectrum disorder prevalence in an epidemiologic sample. *Journal of the American Academy of Child and Adolescent Psychiatry*. https://doi.org/10.1016/j.jaac.2013.12.021

King, B. R., Van Ruitenbeek, P., Leunissen, I., Cuypers, K., Heise, K. F., Santos Monteiro, T., Hermans, L., Levin, O., Albouy, G., Mantini, D., & Swinnen, S. P. (2018). Age-related declines in motor performance are associated with decreased segregation of large-scale resting state brain networks. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhx297

Kleinhans, N. M., Johnson, L. C., Richards, T., Mahurin, R., Greenson, J., Dawson, G., & Aylward, E. (2009). Reduced neural habituation in the amygdala and social impairments in autism spectrum disorders.

American Journal of Psychiatry. https://doi.org/10.1176/appi.ajp.2008.07101681

Kleinhans, N. M., Richards, T., Greenson, J., Dawson, G., & Aylward, E. (2016). Altered dynamics of the fMRI response to faces in individuals with autism. *Journal of autism and developmental disorders*, *46*(1), 232-241.

Kleinhans, N. M., Richards, T., Sterling, L., Stegbauer, K. C., Mahurin, R., Johnson, L. C., Greenson, J., Dawson, G., & Aylward, E. (2008). Abnormal functional connectivity in autism spectrum disorders during face processing. *Brain*. https://doi.org/10.1093/brain/awm334

Kleinhans, N. M., Richards, T., Weaver, K., Johnson, L. C., Greenson, J., Dawson, G., & Aylward, E. (2010). Association between amygdala response to emotional faces and social anxiety in autism spectrum disorders. *Neuropsychologia*, *48*(12), 3665-3670.

Kliemann, D., Richardson, H., Anzellotti, S., Ayyash, D., Haskins, A. J., Gabrieli, J. D. E., & Saxe, R. R. (2018). Cortical responses to dynamic emotional facial expressions generalize across stimuli, and are sensitive to task-relevance, in adults with and without Autism. *Cortex*, *103*, 24–43. https://doi.org/10.1016/j.cortex.2018.02.006

Koshino, H., Kana, R. K., Keller, T. A., Cherkassky, V. L., Minshew, N. J., & Just, M. A. (2008). fMRI investigation of working memory for faces in autism: Visual coding and underconnectivity with frontal areas. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhm054

Koster-Hale, J., Saxe, R., Dungan, J., & Young, L. L. (2013). Decoding moral judgments from neural representations of intentions. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.1207992110

Kracke, Ii. (1994). Developmental prosopagnosia in Asperger syndrome: presentation and discussion of an individual case. *Developmental Medicine & Child Neurology*, *36*(10), 873–886.

Kriegeskorte, N., & Bandettini, P. (2007). Analyzing for information, not activation, to exploit high-resolution fMRI. In *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2007.02.022

Kriegeskorte, N., Formisano, E., Sorger, B., & Goebel, R. (2007). Individual faces elicit distinct response patterns in human anterior temporal cortex. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.0705654104

Kriegeskorte, N., Mur, M., & Bandettini, P. (2008). Representational similarity analysis - connecting the branches of systems neuroscience. *Frontiers in Systems Neuroscience*, *2*(November), 4. https://doi.org/10.3389/neuro.06.004.2008

Kugel, H., Eichmann, M., Dannlowski, U., Ohrmann, P., Bauer, J., Arolt, V., Heindel, W., & Suslow, T. (2008). Alexithymic features and automatic amygdala reactivity to facial emotion. *Neuroscience Letters*, *435*(1), 40–44.

Kylliäinen, A., & Hietanen, J. K. (2006). Skin conductance responses to another person's gaze in children with autism. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-006-0091-4

LaBar, K. S., Crupain, M. J., Voyvodic, J. T., & McCarthy, G. (2003). Dynamic perception of facial affect and identity in the human brain. *Cerebral Cortex*. https://doi.org/10.1093/cercor/13.10.1023

Lacroix, A., Guidetti, M., Rogé, B., & Reilly, J. (2014). Facial emotion recognition in 4- to 8-year-olds with autism spectrum disorder: A developmental trajectory approach. *Research in Autism Spectrum Disorders*, *8*, 1146–1154. doi:10.1016/j.rasd.2014.05.012

Lahaie, A., Mottron, L., Arguin, M., Berthiaume, C., Jemel, B., & Saumier, D. (2006). Face perception in high functioning autistic adults: evidence for superior processing of face parts, not for a configural face-processing deficit. *Neuropsychology*, *20*(1), 30.

Lai, M.-C., & Szatmari, P. (2020). Sex and gender impacts on the behavioural presentation and recognition of autism. *Current Opinion in Psychiatry*, *33*(2), 117–123.

Lau, W. K. W., Leung, M. K., & Lau, B. W. M. (2019). Resting-state abnormalities in Autism Spectrum Disorders: A meta-analysis. *Scientific Reports*. https://doi.org/10.1038/s41598-019-40427-7

Law Smith, M. J., Montagne, B., Perrett, D. I., Gill, M., & Gallagher, L. (2010). Detecting subtle facial emotion recognition deficits in high functioning Autism using dynamic stimuli of varying intensities. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2010.03.008

Lawson, R. P., Aylward, J., White, S., & Rees, G. (2015). A striking reduction of simple loudness adaptation in autism. *Scientific reports*, *5*(1), 1-7.

Lee, L. C., Andrews, T. J., Johnson, S. J., Woods, W., Gouws, A., Green, G. G. R., & Young, A. W. (2010). Neural

responses to rigidly moving faces displaying shifts in social attention investigated with fMRI and MEG. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2009.10.005

Lee Masson, H., Pillet, I., Amelynck, S., Van De Plas, S., Hendriks, M. H. A., Op De Beeck, H., & Boets, B. (2019). Intact neural representations of affective meaning of touch but lack of embodied resonance in autism: a multi-voxel pattern analysis study. *Molecular Autism*. https://doi.org/10.1186/s13229-019-0294-0

Lenth, R. V. (2021). *emmeans: Estimated Marginal Means, aka Least-Squares Means* (R package version 1.6.0.). https://cran.r-project.org/package=emmeans

Leppänen, J. M., & Hietanen, J. K. (2004). Positive facial expressions are recognized faster than negative facial expressions, but why? *Psychological Research*, *69*(1), 22–29.

Leung, D., Ordqvist, A., Falkmer, T., Parsons, R., & Falkmer, M. (2013). Facial emotion recognition and visual search strategies of children with high functioning autism and Asperger syndrome. *Research in Autism Spectrum Disorders*, *7*, 833–844. doi:10.1016/j.rasd.2013.03.009

Leveroni, C. L., Seidenberg, M., Mayer, A. R., Mead, L. A., Binder, J. R., & Rao, S. M. (2000). Neural systems underlying the recognition of familiar and newly learned faces. *Journal of Neuroscience*. https://doi.org/10.1523/jneurosci.20-02-00878.2000

Liu-Shuang, J., Norcia, A. M., & Rossion, B. (2014). An objective index of individual face discrimination in the right occipito-temporal cortex by means of fast periodic oddball stimulation. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2013.10.022

Liu-Shuang, J., Torfs, K., & Rossion, B. (2016). An objective electrophysiological marker of face individualisation impairment in acquired prosopagnosia with fast periodic visual stimulation. *Neuropsychologia*, *83*, 100–113.

Livingston, L. A., Shah, P., & Happé, F. (2019). Compensatory strategies below the behavioural surface in autism: a qualitative study. *The Lancet Psychiatry*, *6*(9), 766–777.

Loomes, R., Hull, L., & Mandy, W. P. L. (2017). What is the male-to-female ratio in autism spectrum disorder? A systematic review and meta-analysis. *Journal of the American Academy of Child & Adolescent Psychiatry*, *56*(6), 466–474.

Lozier, L. M., Vanmeter, J. W., & Marsh, A. A. (2014). Impairments in facial affect recognition associated with autism spectrum disorders: A meta-analysis. *Development and Psychopathology*. https://doi.org/10.1017/S0954579414000479

Luckhardt, C, Jarczok, T. A., & Bender, S. (2014). Elucidating the neurophysiological underpinnings of autism spectrum disorder: New developments. *Journal of Neural Transmission*, *121*(9), 1129–1144.

Luckhardt, Christina, Kröger, A., Cholemkery, H., Bender, S., & Freitag, C. M. (2017). Neural Correlates of Explicit Versus Implicit Facial Emotion Processing in ASD. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-017-3141-1

Lugo-Marín, J., Magán-Maganto, M., Rivero-Santana, A., Cuellar-Pompa, L., Alviani, M., Jenaro-Rio, C., Díez, E., & Canal-Bedia, R. (2019). Prevalence of psychiatric disorders in adults with autism spectrum disorder: A systematic review and meta-analysis. *Research in Autism Spectrum Disorders*, *59*, 22–33.

Magnée, M. J. C. M., de Gelder, B., van Engeland, H., & Kemner, C. (2011). Multisensory integration and attention in Autism Spectrum disorder: Evidence from Event-related potentials. *PLoS ONE*. https://doi.org/10.1371/journal.pone.0024196

Magnée, M. J. C. M., de Gelder, B., van Engeland, H., Kemner, C., Maurice, M. J., de Gelder, B., van Engeland, H., & Chantal Kemner. (2008). Atypical processing of fearful face-voice pairs in Pervasive Developmental Disorder: An ERP study. *Clinical Neurophysiology*. https://doi.org/10.1016/j.clinph.2008.05.005

Malisza, K. L., Clancy, C., Shiloff, D., Holden, J., Jones, C., Paulson, K., ... & Chudley, A. E. (2011). Functional magnetic resonance imaging of facial information processing in children with autistic disorder, attention deficit hyperactivity disorder and typically developing controls.

Mamashli, F., Kozhemiako, N., Khan, S., Nunes, A. S., McGuiggan, N. M., Losh, A., ... & Kenet, T. (2021). Children with autism spectrum disorder show altered functional connectivity and abnormal maturation trajectories in response to inverted faces. *Autism Research*, *14*(6), 1101-1114.

Mayer, E., & Rossion, B. (2007). *Prosopagnosia*.

Mazard, A., Schiltz, C., & Rossion, B. (2006). Recovery from adaptation to facial identity is larger for upright than inverted faces in the human occipito-temporal cortex. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2005.08.015

McPartland, J. C., Dawson, G., Webb, S. J., Panagiotides, H., & Carver, L. J. (2004). Event-related brain potentials reveal anomalies in temporal processing of faces in autism spectrum disorder. *Journal of Child Psychology and Psychiatry*, *45*(7), 1235–1245.

McPartland, J. C., Webb, S. J., Keehn, B., & Dawson, G. (2011). Patterns of visual attention to faces and objects in autism spectrum disorder. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-010-1033-8

McPartland, J. C., Wu, J., Bailey, C. A., Mayes, L. C., Schultz, R. T., & Klin, A. (2011). Atypical neural specialization for social percepts in autism spectrum disorder. *Social Neuroscience*, *6*(5–6), 436–451.

Meza-Concha, N., Arancibia, M., Salas, F., Behar, R., Salas, G., Silva, H., & Escobar, R. (2017). Towards a neurobiological understanding of alexithymia. *Medwave*, *17*(04).

Montagne, B., Kessels, R. P. C., De Haan, E. H. F., & Perrett, D. I. (2007). The emotion recognition task: A paradigm to measure the perception of facial emotional expressions at different intensities. *Perceptual and Motor Skills*. https://doi.org/10.2466/PMS.104.2.589-598

Monteiro, R., Simões, M., Andrade, J., & Castelo Branco, M. (2017). Processing of Facial Expressions in Autism: a Systematic Review of EEG/ERP Evidence. In *Review Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s40489-017-0112-6

Moradi, F., Buračas, G. T., & Buxton, R. B. (2012). Attention strongly increases oxygen metabolic response to stimulus in primary visual cortex. *Neuroimage*, *59*(1), 601–607.

Morie, K. P., Jackson, S., Potenza, M. N., & Dritschel, B. (2019). Mood disorders in high functioning autism: The importance of alexithymia and emotional regulation. *Journal of Autism and Developmental Disorders*, *49*(7), 2935–2945.

Moscovitch, M., Winocur, G., & Behrmann, M. (1997). What is special about face recognition? Nineteen experiments on a person with visual object agnosia and dyslexia but normal face recognition. *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/jocn.1997.9.5.555

Mottron, L., Dawson, M., Soulières, I., Hubert, B., & Burack, J. (2006). Enhanced perceptual functioning in autism: An update, and eight principles of autistic perception. *Journal of Autism and Developmental Disorders*, *36*(1), 27–43. https://doi.org/10.1007/s10803-005-0040-7

Murphy, E. R., Foss-Feig, J., Kenworthy, L., Gaillard, W. D., & Vaidya, C. J. (2012). Atypical Functional Connectivity of the Amygdala in Childhood Autism Spectrum Disorders during Spontaneous Attention to Eye-Gaze. *Autism Research and Treatment*. https://doi.org/10.1155/2012/652408

Nakamura, K., Kawashima, R., Sato, N., Nakamura, A., Sugiura, M., Kato, T., Hatano, K., Ito, K., Fukuda, H., Schormann, T., & Zilles, K. (2000). Functional delineation of the human occipitotemporal areas related to face and scene processing a PET study. *Brain*. https://doi.org/10.1093/brain/123.9.1903

Nemrodov, D., Behrmann, M., Niemeier, M., Drobotenko, N., & Nestor, A. (2019). Multimodal evidence on shape and surface information in individual face processing. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2018.09.083

Nestor, A., Plaut, D. C., & Behrmann, M. (2011). Unraveling the distributed neural code of facial identity through spatiotemporal pattern analysis. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.1102433108

Nestor, A., Plaut, D. C., & Behrmann, M. (2016). Feature-based face representations and image reconstruction from behavioral and neural data. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.1514551112

Neuhaus, E., Kresse, A., Faja, S., Bernier, R. A., & Webb, S. J. (2016). Face processing among twins with and without autism: social correlates and twin concordance. *Social Cognitive and Affective Neuroscience*, *11*(1), 44–54.

Nichols, D. F., Betts, L. R., & Wilson, H. R. (2010). Decoding of faces and face components in face-sensitive human visual cortex. *Frontiers in Psychology*. https://doi.org/10.3389/fpsyg.2010.00028

Noens, I., De la Marche, W., & Scholte, E. (2012). *SRS-A - Screeningslijst voor autismespectrumstoornissen. Handleiding.* Hogrefe.

Nomi, J. S., & Uddin, L. Q. (2015). Face processing in autism spectrum disorders: From brain regions to brain networks. *Neuropsychologia*, *71*, 201–216. https://doi.org/10.1016/j.neuropsychologia.2015.03.029

Norcia, A. M., Gregory Appelbaum, L., Ales, J. M., Cottereau, B. R., & Rossion, B. (2015). The steady-state visual evoked potential in vision research: A review. *Journal of Vision*. https://doi.org/10.1167/15.6.4

Norman, K. A., Polyn, S. M., Detre, G. J., & Haxby, J. V. (2006). Beyond mind-reading: multi-voxel pattern analysis of fMRI data. In *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2006.07.005

O'Brien, J., Spencer, J., Girges, C., Johnston, A., & Hill, H. (2014). Impaired perception of facial motion in autism spectrum disorder. *PLoS ONE*. https://doi.org/10.1371/journal.pone.0102173

O'Connor, K., Hamm, J. P., & Kirk, I. J. (2005). The neurophysiological correlates of face processing in adults and children with Asperger's syndrome. *Brain and Cognition*. https://doi.org/10.1016/j.bandc.2005.05.004

O'Connor, K., Hamm, J. P., & Kirk, I. J. (2007). Neurophysiological responses to face, facial regions and objects in adults with Asperger's syndrome: An ERP investigation. *International Journal of Psychophysiology*. https://doi.org/10.1016/j.ijpsycho.2006.12.001

O'Connor, R. C., Wetherall, K., Cleare, S., McClelland, H., Melson, A. J., Niedzwiedz, C. L., O'Carroll, R. E., O'Connor, D. B., Platt, S., & Scowcroft, E. (2021). Mental health and well-being during the COVID-19 pandemic: longitudinal analyses of adults in the UK COVID-19 Mental Health & Wellbeing study. *The British Journal of Psychiatry*, *218*(6), 326–333.

O'Hearn, K., Schroer, E., Minshew, N., & Luna, B. (2010). Lack of developmental improvement on a face memory task during adolescence in autism. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2010.08.024

O'Neil, E. B., Hutchison, R. M., McLean, D. A., & Köhler, S. (2014). Resting-state fMRI reveals functional connectivity between face-selective perirhinal cortex and the fusiform face area related to face inversion. *Neuroimage*, *92*, 349-355.

O'Toole, A. J., Roark, D. A., & Abdi, H. (2002). Recognizing moving faces: A psychological and neural synthesis. In *Trends in Cognitive Sciences*. https://doi.org/10.1016/S1364-6613(02)01908-3

Oakley, B. F. M., Jones, E. J. H., Crawley, D., Charman, T., Buitelaar, J., Tillmann, J., Murphy, D. G., & Loth, E. (2020). Alexithymia in autism: cross-sectional and longitudinal associations with social-communication difficulties, anxiety and depression symptoms. *Psychological Medicine*, 1–13.

Oruc, I., Shafai, F., & Iarocci, G. (2018). Link Between Facial Identity and Expression Abilities Suggestive of Origins of Face Impairments in Autism: Support for the Social-Motivation Hypothesis. *Psychological Science*. https://doi.org/10.1177/0956797618795471

Palermo, R., Jeffery, L., Lewandowsky, J., Fiorentini, C., Irons, J. L., Dawel, A., ... & Rhodes, G. (2018). Adaptive face coding contributes to individual differences in facial expression recognition independently of affective factors. *Journal of Experimental Psychology: Human Perception and Performance*, *44*(4), 503.

Pegado, F., Hendriks, M. H. A., Amelynck, S., Daniels, N., Bulthé, J., Masson, H. L., Boets, B., & de Beeck, H. O. (2018). Neural Representations Behind 'Social Norm' Inferences In Humans. *Scientific Reports*. https://doi.org/10.1038/s41598-018-31260-5

Pegado, F., Hendriks, M. H. A., Amelynck, S., Daniels, N., Steyaert, J., Boets, B., & Op de Beeck, H. (2020). Adults with high functioning autism display idiosyncratic behavioral patterns, neural representations and connectivity of the 'Voice Area' while judging the appropriateness of emotional vocal reactions. *Cortex*. https://doi.org/10.1016/j.cortex.2019.11.008

Pelphrey, K. A., Morris, J. P., Mccarthy, G., & Labar, K. S. (2007). Perception of dynamic changes in facial affect and identity in autism. *Social Cognitive and Affective Neuroscience*, *2*(2), 140–149. https://doi.org/10.1093/scan/nsm010

Persico, A. M., & Napolioni, V. (2013). Autism genetics. In *Behavioural Brain Research*. https://doi.org/10.1016/j.bbr.2013.06.012

Pessoa, L., McKenna, M., Gutierrez, E., & Ungerleider, L. G. (2002). Neural processing of emotional faces requires attention. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.172403899

Peters, L., Polspoel, B., Op de Beeck, H., & De Smedt, B. (2016). Brain activity during arithmetic in symbolic and non-symbolic formats in 9-12 year old children. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2016.04.001

Philip, R. C. M., Dauvermann, M. R., Whalley, H. C., Baynham, K., Lawrie, S. M., & Stanfield, A. C. (2012). A systematic review and meta-analysis of the fMRI investigation of autism spectrum disorders. In *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2011.10.008

Pierce, K. (2001). Face processing occurs outside the fusiform `face area' in autism: evidence from functional MRI. *Brain*. https://doi.org/10.1093/brain/124.10.2059

Pierce, K., & Redcay, E. (2008). Fusiform function in children with an autism spectrum disorder is a matter of "who". *Biological psychiatry*, *64*(7), 552-560.

Pitcher, D. (2014). Facial expression recognition takes longer in the posterior superior temporal sulcus than in the occipital face area. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.5038-13.2014

Pitcher, D., Charles, L., Devlin, J. T., Walsh, V., & Duchaine, B. (2009). Triple Dissociation of Faces, Bodies, and Objects in Extrastriate Cortex. *Current Biology*. https://doi.org/10.1016/j.cub.2009.01.007

Pitcher, D., Dilks, D. D., Saxe, R. R., Triantafyllou, C., & Kanwisher, N. (2011). Differential selectivity for dynamic versus static information in face-selective cortical regions. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2011.03.067

Pitcher, D., Duchaine, B., & Walsh, V. (2014). Combined TMS and fMRI reveal dissociable cortical pathways for dynamic and static face perception. *Current Biology*. https://doi.org/10.1016/j.cub.2014.07.060

Pitcher, D., Garrido, L., Walsh, V., & Duchaine, B. C. (2008). Transcranial magnetic stimulation disrupts the perception and embodiment of facial expressions. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.1450-08.2008

Pitcher, D., Goldhaber, T., Duchaine, B., Walsh, V., & Kanwisher, N. (2012). Two critical and functionally distinct stages of face and body perception. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.2624-12.2012

Pitcher, D., & Ungerleider, L. G. (2021). Evidence for a Third Visual Pathway Specialized for Social Perception. In *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2020.11.006

Pitcher, D., Walsh, V., & Duchaine, B. (2011). The role of the occipital face area in the cortical face perception network. In *Experimental Brain Research*. https://doi.org/10.1007/s00221-011-2579-1

Poljac, E., Poljac, E., & Wagemans, J. (2013). Reduced accuracy and sensitivity in the perception of emotional facial expressions in individuals with high autism spectrum traits. *Autism*. https://doi.org/10.1177/1362361312455703

Poncet, F., Baudouin, J.-Y., Dzhelyova, M. P., Rossion, B., & Leleu, A. (2019). Rapid and automatic discrimination between facial expressions in the human brain. *Neuropsychologia*, *129*, 47–55.

Poquérusse, J., Pastore, L., Dellantonio, S., & Esposito, G. (2018). Alexithymia and autism spectrum disorder: a complex relationship. *Frontiers in Psychology*, *9*, 1196.

Proverbio, A. M., Brignone, V., Matarazzo, S., Del Zotto, M., & Zani, A. (2006). Gender differences in hemispheric asymmetry for face processing. *BMC Neuroscience*, *7*(1), 1–10.

Puce, A., Allison, T., Bentin, S., Gore, J. C., & McCarthy, G. (1998). Temporal cortex activation in humans viewing eye and mouth movements. *Journal of Neuroscience*. https://doi.org/10.1523/jneurosci.18-06-02188.1998

Pyles, J. A., Verstynen, T. D., Schneider, W., & Tarr, M. J. (2013). Explicating the Face Perception Network with White Matter Connectivity. *PLoS ONE*. https://doi.org/10.1371/journal.pone.0061611

R Core Team, R. (2020). *R: A language and environment for statistical computing*.

R Development Core Team, R. (2012). R: A Language and Environment for Statistical Computing. In *R Foundation for Statistical Computing, version 3.4.3. Vienna, Austria*. https://doi.org/10.1007/978-3-540-74686-7

Reker, M., Ohrmann, P., Rauch, A. V, Kugel, H., Bauer, J., Dannlowski, U., Arolt, V., Heindel, W., & Suslow, T. (2010). Individual differences in alexithymia and brain response to masked emotion faces. *Cortex*, *46*(5), 658–667.

Retter, T. L., & Rossion, B. (2016). Uncovering the neural magnitude and spatio-temporal dynamics of natural image categorization in a fast visual stream. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2016.07.028

Richer, J. (1976). The social-avoidance behaviour of autistic children. *Animal Behaviour*. https://doi.org/10.1016/S0003-3472(76)80020-6

Richler, J. J., & Gauthier, I. (2014). *Psychological Bulletin A Meta-Analysis and Review of Holistic Face Processing A Meta-Analysis and Review of Holistic Face Processing*. *140*(5), 1281–1302. https://doi.org/10.1037/a0037004.A

Riddoch, M. J., Johnston, R. A., Bracewell, R. M., Boutsen, L., & Humphreys, G. W. (2008). Are faces special? A case of pure prosopagnosia. *Cognitive Neuropsychology*. https://doi.org/10.1080/02643290801920113

Robertson, C. E., Thomas, C., Kravitz, D. J., Wallace, G. L., Baron-Cohen, S., Martin, A., & Baker, C. I. (2014). Global motion perception deficits in autism are reflected as early as primary visual cortex. *Brain*. https://doi.org/10.1093/brain/awu189

Robinson, J. E. (2007). *Look Me in the Eye: My Life with Asperger's*. Crown Publishers.

Rossion, B. (2013). The composite face illusion: A whole window into our understanding of holistic face perception. In *Visual Cognition*. https://doi.org/10.1080/13506285.2013.772929

Rossion, B. (2014). Understanding individual face discrimination by means of fast periodic visual stimulation. In *Experimental Brain Research*. https://doi.org/10.1007/s00221-014-3934-9

Rossion, B., Caldara, R., Seghier, M., Schuller, A., Lazeyras, F., & Mayer, E. (2003). *A network of occipito-temporal face-sensitive areas besides the right middle fusiform gyrus is necessary for normal face processing*. https://doi.org/10.1093/brain/awg241

Rossion, B., Gauthier, I., Tarr, M. J., Despland, P., Bruyer, R., Linotte, S., & Crommelinck, M. (2000). The N170 occipito-temporal component is delayed and enhanced to inverted faces but not to inverted objects: an electrophysiological account of face-specific processes in the human brain. *Neuroreport*, *11*(1), 69-72.

Rossion, B., Joyce, C. A., Cottrell, G. W., & Tarr, M. J. (2003). Early lateralization and orientation tuning for face, word, and object processing in the visual cortex. *Neuroimage*, *20*(3), 1609–1624.

Rossion, B., & Michel, C. (2018). Normative accuracy and response time data for the computerized Benton Facial Recognition Test (BFRT-c). *Behavior Research Methods*. https://doi.org/10.3758/s13428-018-1023-x

Rossion, B., Prieto, E. A., Boremanse, A., Kuefner, D., & Van Belle, G. (2012). A steady-state visual evoked potential approach to individual face perception: Effect of inversion, contrast-reversal and temporal dynamics. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2012.08.033

Rossion, B., Torfs, K., Jacques, C., & Liu-Shuang, J. (2015). Fast periodic presentation of natural images reveals a robust face-selective electrophysiological response in the human brain. *Journal of Vision*, *15*(1), 18.

Rotshtein, P., Henson, R. N. A., Treves, A., Driver, J., & Dolan, R. J. (2005). Morphing Marilyn into Maggie dissociates physical and identity face representations in the brain. *Nature Neuroscience*. https://doi.org/10.1038/nn1370

Royer, J., Blais, C., Charbonneau, I., Déry, K., Tardif, J., Duchaine, B., Gosselin, F., & Fiset, D. (2018). Greater reliance on the eye region predicts better face recognition ability. *Cognition*. https://doi.org/10.1016/j.cognition.2018.08.004

Rump, K. M., Giovannelli, J. L., Minshew, N. J., & Strauss, M. S. (2009). The development of emotion recognition in individuals with autism. *Child Development*. https://doi.org/10.1111/j.1467-8624.2009.01343.x

Russell, G., Mandy, W., Elliott, D., White, R., Pittwood, T., & Ford, T. (2019). Selection bias on intellectual ability in autism research: A cross-sectional review and meta-analysis. *Molecular Autism*, *10*(1), 1–10.

Rutiku, R., Aru, J., & Bachmann, T. (2016). General markers of conscious visual perception and their timing. *Frontiers in Human Neuroscience*, *10*, 23.

Sabatinelli, D., Fortune, E. E., Li, Q., Siddiqui, A., Krafft, C., Oliver, W. T., Beck, S., & Jeffries, J. (2011). NeuroImage Emotional perception : Meta-analyses of face and natural scene processing. *NeuroImage*, *54*(3), 2524–2533. https://doi.org/10.1016/j.neuroimage.2010.10.011

Sadeh, B., Podlipsky, I., Zhdanov, A., & Yovel, G. (2010). Event-related potential and functional MRI measures of face-selectivity are highly correlated: A simultaneous ERP-fMRI investigation. *Human Brain Mapping*. https://doi.org/10.1002/hbm.20952

Sadr, J., Jarudi, I., & Sinha, P. (2003). The role of eyebrows in face recognition. *Perception*. https://doi.org/10.1068/p5027

Samson, F., Mottron, L., Soulières, I., & Zeffiro, T. A. (2012). Enhanced visual functioning in autism: An ALE meta-analysis. *Human Brain Mapping*. https://doi.org/10.1002/hbm.21307

Santos, A., Mier, D., Kirsch, P., & Meyer-Lindenberg, A. (2011). Evidence for a general face salience signal in human amygdala. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2010.11.024

Sapey-Triomphe, L. A., Boets, B., Van Eylen, L., Noens, I., Sunaert, S., Steyaert, J., & Wagemans, J. (2020). Ventral stream hierarchy underlying perceptual organization in adolescents with autism. *NeuroImage: Clinical*. https://doi.org/10.1016/j.nicl.2020.102197

Sasson, N. J., Shasteen, J. R., & Pinkham, A. E. (2016). Brief report: Reduced prioritization of facial threat in

adults with autism. *Journal of Autism and Developmental Disorders*, *46*(4), 1471–1476.

Sato, W., Kochiyama, T., Yoshikawa, S., Naito, E., & Matsumura, M. (2004). Enhanced neural activity in response to dynamic facial expressions of emotion: An fMRI study. *Cognitive Brain Research*. https://doi.org/10.1016/j.cogbrainres.2004.01.008

Sato, W., Toichi, M., Uono, S., & Kochiyama, T. (2012). Impaired social brain network for processing dynamic facial expressions in autism spectrum disorders. *BMC Neuroscience*. https://doi.org/10.1186/1471-2202-13-99

Scherer, K. R., & Scherer, U. (2011). Assessing the Ability to Recognize Facial and Vocal Expressions of Emotion: Construction and Validation of the Emotion Recognition Index. *Journal of Nonverbal Behavior*. https://doi.org/10.1007/s10919-011-0115-4

Schultz, J., & Pilz, K. S. (2009). Natural facial motion enhances cortical responses to faces. *Experimental Brain Research*. https://doi.org/10.1007/s00221-009-1721-9

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

Schyns, P. G., Petro, L. S., & Smith, M. L. (2009). Transmission of facial expressions of emotion co-evolved with their efficient decoding in the brain: Behavioral and brain evidence. *PLoS ONE*. https://doi.org/10.1371/journal.pone.0005625

Sekuler, A. B., Gaspar, C. M., Gold, J. M., & Bennett, P. J. (2004). Inversion leads to quantitative, not qualitative, changes in face processing. *Current Biology*. https://doi.org/10.1016/j.cub.2004.02.028

Shephard, E., Milosavljevic, B., Mason, L., Elsabbagh, M., Tye, C., Gliga, T., ... & Volein, A. (2020). Neural and behavioural indices of face processing in siblings of children with autism spectrum disorder (ASD): A longitudinal study from infancy to mid-childhood. *Cortex*, *127*, 162-179.

Simion, F., & Giorgio, E. Di. (2015). Face perception and processing in early infancy: inborn predispositions and developmental changes. *Frontiers in Psychology*, *6*, 969.

Simmons, D. R., Robertson, A. E., McKay, L. S., Toal, E., McAleer, P., & Pollick, F. E. (2009). Vision in autism spectrum disorders. *Vision Research*, *49*(22), 2705–2739. https://doi.org/10.1016/j.visres.2009.08.005

Singmann, H., Bolker, B., Westfall, J., & Aust, F. (2018). afex: analysis of factorial experiments. R package version 0.16-1. *R Package Version 0.20-2*.

Singmann, H., Bolker, B., Westfall, J., Aust, F., & Ben-Shachar, M. S. (2021). *afex: Analysis of factorial experiments*. (R package version 0.28-1). https://cran.r-project.org/package=afex

Smith, M. L., Cottrell, G. W., Gosselin, F., & Schyns, P. G. (2005). Transmitting and decoding facial expressions. *Psychological Science*. https://doi.org/10.1111/j.0956-7976.2005.00801.x

Sorger, B., Goebel, R., Schiltz, C., & Rossion, B. (2007). Understanding the functional neuroanatomy of acquired prosopagnosia. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2006.09.051

Spezio, M. L., Adolphs, R., Hurley, R. S. E., & Piven, J. (2007). Abnormal use of facial information in high functioning autism. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-006-0232-9

Spielberger, C. D. (1983). *Manual for the State-Trait Anxiety Inventory STAI (form Y)(" self-evaluation questionnaire")*.

Spiridon, M., Fischl, B., & Kanwisher, N. (2006). Location and spatial profile of category-specific regions in human extrastriate cortex. *Human Brain Mapping*. https://doi.org/10.1002/hbm.20169

Sprengelmeyer, R., Rausch, M., Eysel, U. T., & Przuntek, H. (1998). Neural structures associated with recognition of facial expressions of basic emotions. *Proceeding of the Royal Society London B Biological Science*, *265*, 1927–1931. https://doi.org/10.1098/rspb.1998.0522

Steeves, J. K. E., Culham, J. C., Duchaine, B. C., Pratesi, C. C., Valyear, K. F., Schindler, I., Humphrey, G. K., Milner, A. D., & Goodale, M. A. (2006). The fusiform face area is not sufficient for face recognition: Evidence from a patient with dense prosopagnosia and no occipital face area. *Neuropsychologia*. https://doi.org/10.1016/j.neuropsychologia.2005.06.013

Sterling, L., Dawson, G., Webb, S., Murias, M., Munson, J., Panagiotides, H., & Aylward, E. (2008). The role of face familiarity in eye tracking of faces by individuals with autism spectrum disorders. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-008-0550-1

Sugiura, M., Kawashima, R., Nakamura, K., Sato, N., Nakamura, A., Kato, T., Hatano, K., Schormann, T., Zilles, K., Sato, K., Ito, K., & Fukuda, H. (2001). Activation reduction in anterior temporal cortices during repeated recognition of faces of personal acquaintances. *NeuroImage*. https://doi.org/10.1006/nimg.2001.0747

Sugiura, M., Mano, Y., Sasaki, A., & Sadato, N. (2011). Beyond the memory mechanism: Person-selective and nonselective processes in recognition of personally familiar faces. *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/jocn.2010.21469

Summerfield, C., Trittschuh, E. H., Monti, J. M., Mesulam, M. M., & Egner, T. (2008). Neural repetition suppression reflects fulfilled perceptual expectations. *Nature Neuroscience*, *11*(9), 1004–1006. https://doi.org/10.1038/nn.2163

Supekar, K., Uddin, L. Q., Khouzam, A., Phillips, J., Gaillard, W. D., Kenworthy, L. E., Yerys, B. E., Vaidya, C. J., & Menon, V. (2013). Brain Hyperconnectivity in Children with Autism and its Links to Social Deficits. *Cell Reports*. https://doi.org/10.1016/j.celrep.2013.10.001

Swartz, J. R., Wiggins, J. L., Carrasco, M., Lord, C., & Monk, C. S. (2013). Amygdala habituation and prefrontal functional connectivity in youth with autism spectrum disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*. https://doi.org/10.1016/j.jaac.2012.10.012

Tam, F. I., King, J. A., Geisler, D., Korb, F. M., Sareng, J., Ritschel, F., ... & Ehrlich, S. (2017). Altered behavioral and amygdala habituation in high functioning adults with autism spectrum disorder: an fMRI study. *Scientific reports*, *7*(1), 1-9.

Tanaka, J. W. (2001). The entry point of face recognition: evidence for face expertise. *Journal of Experimental Psychology: General*, *130*(3), 534–543.

Tanaka, J. W., & Farah, M. J. (1993). Parts and Wholes in Face Recognition. *The Quarterly Journal of Experimental Psychology Section A*. https://doi.org/10.1080/14640749308401045

Tanaka, J. W., & Gauthier, I. (1997). Expertise in Object and Face Recognition. *Psychology of Learning and Motivation - Advances in Research and Theory*, *36*(C), 83–125. https://doi.org/10.1016/S0079-7421(08)60282-0

Tanaka, J. W., & Simonyi, D. (2016). The "parts and wholes" of face recognition: A review of the literature. *Quarterly Journal of Experimental Psychology*. https://doi.org/10.1080/17470218.2016.1146780

Tanaka, J. W., & Sung, A. (2016). The "Eye Avoidance" Hypothesis of Autism Face Processing. *Journal of Autism and Developmental Disorders*, *46*, 1538–1552. https://doi.org/10.1007/s10803-013-1976-7

Tanaka, J. W., Wolf, J. M., Klaiman, C., Koenig, K., Cockburn, J., Herlihy, L., Brown, C., Stahl, S. S., South, M., & McPartland, J. C. (2012). The perception and identification of facial emotions in individuals with autism spectrum disorders using the Let's Face It! Emotion Skills Battery. *Journal of Child Psychology and Psychiatry*, *53*(12), 1259–1267.

Tang, J., Falkmer, M., Horlin, C., Tan, T., Vaz, S., & Falkmer, T. (2015). Face Recognition and Visual Search Strategies in Autism Spectrum Disorders: Amending and Extending a Recent Review by Weigelt et al. *PLOS ONE*, *10*(8), e0134439. https://doi.org/10.1371/journal.pone.0134439

Tavares, P. P., Mouga, S. S., Oliveira, G. G., & Castelo-Branco, M. (2016). Preserved face inversion effects in adults with autism spectrum disorder: An event-related potential study. *NeuroReport*. https://doi.org/10.1097/WNR.0000000000000576

Taylor, G. J. (1984). Alexithymia: concept, measurement, and implications for treatment. *The American Journal of Psychiatry*.

Taylor, G. J. (1994). The alexithymia construct: conceptualization, validation, and relationship with basic dimensions of personality. *New Trends in Experimental & Clinical Psychiatry*.

Taylor, M. J., Arsalidou, M., Bayless, S. J., Morris, D., Evans, J. W., & Barbeau, E. J. (2009). Neural correlates of personally familiar faces: Parents, partner and own faces. *Human Brain Mapping*. https://doi.org/10.1002/hbm.20646

The Mathworks Inc., M. (2020). *MATLAB Version 2020b*. The MathWorks Inc.

Tick, B., Bolton, P., Happé, F., Rutter, M., & Rijsdijk, F. (2016). Heritability of autism spectrum disorders: A meta-analysis of twin studies. *Journal of Child Psychology and Psychiatry and Allied Disciplines*. https://doi.org/10.1111/jcpp.12499

Tovée, M. J. (1998). Face processing: getting by with a little help from its friends. *Current Biology*, 317–320. https://doi.org/10.1016/s0960-9822(98)70197-6

Tracy, J. L., Robins, R. W., Schriber, R. A., & Solomon, M. (2011). Is emotion recognition impaired in individuals

with autism spectrum disorders? *Journal of Autism and Developmental Disorders*, *41*, 102–109. doi:10.1007/s10803-010-1030-y

Tranel, D., Damasio, H., & Damasio, A. R. (1997). A neural basis for the retrieval of conceptual knowledge. *Neuropsychologia*. https://doi.org/10.1016/S0028-3932(97)00085-7

Trautmann, S. A., Fehr, T., & Herrmann, M. (2009). Emotions in motion: Dynamic compared to static facial expressions of disgust and happiness reveal more widespread emotion-specific activations. *Brain Research*. https://doi.org/10.1016/j.brainres.2009.05.075

Trijsburg, R. W., Passchier, J., Duivenvoorden, H., & Bagby, R. M. (1997). The Toronto Alexithymia Scale (Dutch version). *Rotterdam: Department of Medical Psychology and Psychotherapy, Erasmus University*.

Tseng, Y. L., Yang, H. H., Savostyanov, A. N., Chien, V. S. C., & Liou, M. (2015). Voluntary attention in Asperger's syndrome: Brain electrical oscillation and phase-synchronization during facial emotion recognition. *Research in Autism Spectrum Disorders*. https://doi.org/10.1016/j.rasd.2015.01.003

Tye, C., Asherson, P., Ashwood, K. L., Azadi, B., Bolton, P., & McLoughlin, G. (2014). Attention and inhibition in children with ASD, ADHD and co-morbid ASD+ ADHD: an event-related potential study. *Psychological medicine*, *44*(5), 1101-1116.

Uljarevic, M., & Hamilton, A. (2013). Recognition of emotions in autism: A formal meta-analysis. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-012-1695-5

Ungerleider, L. G., & Mishkin, M. (1982). Two cortical visual systems. In D. J. Ingle, M. A. Goodale, & R. J. . Mansfield (Eds.), *Analysis of Visual Behavior* (pp. 549–586). MIT Press. https://doi.org/10.2139/ssrn.1353746

Van de Cruys, S., Evers, K., Van der Hallen, R., van Eylen, L., Boets, B., de-Wit, L., & Wagemans, J. (2014). Precise minds in uncertain worlds: predictive coding in autism. *Psychological Review*, *121*(4), 649–675. https://doi.org/10.1037/a0037665

Van der Does, A. J. W. (2002). *BDI-II-NL. Handleiding. De Nederlandse versie van de Beck Depression Inventory.* (Second edi). Harcourt Test Publishers.

Van der Donck, S., Dzhelyova, M., Vettori, S., Mahdi, S. S., Claes, P., Steyaert, J., & Boets, B. (2020). Rapid neural categorization of angry and fearful faces is specifically impaired in boys with autism spectrum disorder. *Journal of Child Psychology and Psychiatry and Allied Disciplines*. https://doi.org/10.1111/jcpp.13201

Van der Donck, S., Dzhelyova, M., Vettori, S., Thielen, H., Steyaert, J., Rossion, B., & Boets, B. (2019). Fast Periodic Visual Stimulation EEG Reveals Reduced Neural Sensitivity to Fearful Faces in Children with Autism. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-019-04172-0

Van der Ploeg, H. M. (1980). Validity of the Zelf-Beoordelings-Vragenlijst (A Dutch version of the Spielberger State-Trait Anxiety Inventory). *Nederlands Tijdschrift Voor de Psychologie En Haar Grensgebieden*, *35*(4), 243–249.

Van der Ploeg, H. M. (1982). De zelf-beoordelings vragenlijst (STAI-DY). *Tijdschr Psychiatr*, *24*, 576–588.

Van Drenth, A. (2018). Rethinking the origins of autism: Ida Frye and the unraveling of children's inner world in the Netherlands in the late 1930s. *Journal of the History of the Behavioral Sciences*. https://doi.org/10.1002/jhbs.21884

Van Krevelen, D. A. (1952). Een geval van "early infantile autism". *Nederlands Tijdschrift Voor Geneeskunde*.

Van Meel, C., Baeck, A., Gillebert, C. R., Wagemans, J., & Op de Beeck, H. P. (2019). The representation of symmetry in multi-voxel response patterns and functional connectivity throughout the ventral visual stream. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2019.02.030

Vasa, R. A., Mostofsky, S. H., & Ewen, J. B. (2016). The disrupted connectivity hypothesis of autism spectrum disorders: time for the next phase in research. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *1*(3), 245–252.

Ventura, P., Carmo, J. C., Souza, C., Martins, F., Leite, I., Pinho, S., Barahona-Correa, B., & Filipe, C. N. (2018). Holistic processing of faces is intact in adults with autism spectrum disorder. *Visual Cognition*, *26*(1), 13–24.

Vettori, S., Dzhelyova, M., Van der Donck, S., Jacques, C., Steyaert, J., Rossion, B., & Boets, B. (2019). Reduced neural sensitivity to rapid individual face discrimination in autism spectrum disorder. *NeuroImage: Clinical*. https://doi.org/10.1016/j.nicl.2018.101613

Vettori, S., Jacques, C., Boets, B., & Rossion, B. (2019). Can the N170 Be Used as an Electrophysiological Biomarker Indexing Face Processing Difficulties in Autism Spectrum Disorder? In *Biological Psychiatry:*

Cognitive Neuroscience and Neuroimaging. https://doi.org/10.1016/j.bpsc.2018.07.015

Vettori, S., Van der Donck, S., Nys, J., Moors, P., Van Wesemael, T., Steyaert, J., ... & Boets, B. (2020). Combined frequency-tagging EEG and eye-tracking measures provide no support for the "excess mouth/diminished eye attention" hypothesis in autism. *Molecular autism, 11*(1), 1-22.

Wallace, S., Coleman, M., & Bailey, A. (2008). Face and object processing in autism spectrum disorders. *Autism Research*. https://doi.org/10.1002/aur.7

Wang, Q., Lu, L., Zhang, Q., Fang, F., Zou, X., & Yi, L. (2018). Eye avoidance in young children with autism spectrum disorder is modulated by emotional facial expressions. *Journal of Abnormal Psychology*, *127*(7), 722.

Wang, S., Tudusciuc, O., Mamelak, A. N., Ross, I. B., Adolphs, R., & Rutishauser, U. (2014). Neurons in the human amygdala selective for perceived emotion. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.1323342111

Webb, S. J., Dawson, G., Bernier, R., & Panagiotides, H. (2006). ERP evidence of atypical face processing in young children with autism. *Journal of autism and developmental disorders*, *36*(7), 881.

Webb, S. J., Jones, E. J., Merkle, K., Namkung, J., Toth, K., Greenson, J., ... & Dawson, G. (2010). Toddlers with elevated autism symptoms show slowed habituation to faces. *Child Neuropsychology*, *16*(3), 255-278.

Webb, S. J., Merkle, K., Murias, M., Richards, T., Aylward, E., & Dawson, G. (2012). ERP responses differentiate inverted but not upright face processing in adults with ASD. *Social Cognitive and Affective Neuroscience*. https://doi.org/10.1093/scan/nsp002

Wegrzyn, M., Riehle, M., Labudda, K., Woermann, F., Baumgartner, F., Pollmann, S., Bien, C. G., & Kissler, J. (2015). Investigating the brain basis of facial expression perception using multi-voxel pattern analysis. *Cortex*, *69*, 131–140. https://doi.org/10.1016/j.cortex.2015.05.003

Weigelt, S., Koldewyn, K., & Kanwisher, N. (2012). Face identity recognition in autism spectrum disorders: A review of behavioral studies. *Neuroscience and Biobehavioral Reviews*, *36*(3), 1060–1084. https://doi.org/10.1016/j.neubiorev.2011.12.008

Whitaker, L. R., Simpson, A., & Roberson, D. (2017). Brief Report: Is Impaired Classification of Subtle Facial Expressions in Children with Autism Spectrum Disorders Related to Atypical Emotion Category Boundaries? *Journal of Autism and Developmental Disorders*, *47*(8), 2628–2634. doi:10.1007/s10803-017-3174-5

Wicker, B., Fonlupt, P., Hubert, B., Tardif, C., Gepner, B., & Deruelle, C. (2008). Abnormal cerebral effective connectivity during explicit emotional processing in adults with autism spectrum disorder. *Social Cognitive and Affective Neuroscience*, *3*(2), 135–143. https://doi.org/10.1093/scan/nsn007

Wicker, B., Michel, F., Henaff, M. A., & Decety, J. (1998). Brain regions involved in the perception of gaze: A pet study. *NeuroImage*. https://doi.org/10.1006/nimg.1998.0357

Wingenbach, T. S. H., Ashwin, C., & Brosnan, M. (2017). Diminished sensitivity and specificity at recognising facial emotional expressions of varying intensity underlie emotion-specific recognition deficits in autism spectrum disorders. *Research in Autism Spectrum Disorders*. https://doi.org/10.1016/j.rasd.2016.11.003

Winston, J. S., Henson, R. N. A., Fine-Goulden, M. R., & Dolan, R. J. (2004). fMRI-adaptation reveals dissociable neural representations of identity and expression in face perception. *Journal of Neurophysiology*. https://doi.org/10.1152/jn.00155.2004

Wong, T. K. W., Fung, P. C. W., Chua, S. E., & McAlonan, G. M. (2008). Abnormal spatiotemporal processing of emotional facial expressions in childhood autism: Dipole source analysis of event-related potentials. *European Journal of Neuroscience*. https://doi.org/10.1111/j.1460-9568.2008.06328.x

Xu, X., & Biederman, I. (2010). Loci of the release from fMRI adaptation for changes in facial expression, identity, and viewpoint. *Journal of Vision*. https://doi.org/10.1167/10.14.36

Yankouskaya, A., Stolte, M., Moradi, Z., Rotshtein, P., & Humphreys, G. (2017). Integration of identity and emotion information in faces: fMRI evidence. *Brain and Cognition*, *116*, 29–39. https://doi.org/10.1016/j.bandc.2017.05.004

Yin, R. K. (1969). Looking at upide-down faces. *Journal of Experimental Psychology*. https://doi.org/10.1037/h0027474

Young, A. W., & Bruce, V. (2011). Understanding person perception. *British Journal of Psychology*. https://doi.org/10.1111/j.2044-8295.2011.02045.x

Yovel, G., & Kanwisher, N. (2005). The neural basis of the behavioral face-inversion effect. *Current Biology*.

https://doi.org/10.1016/j.cub.2005.10.072

Zhang, H., Japee, S., Nolan, R., Chu, C., Liu, N., & Ungerleider, L. G. (2016). Face-selective regions differ in their ability to classify facial expressions. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2016.01.045

Zhang, H., Tian, J., Liu, J., Li, J., & Lee, K. (2009). Intrinsically organized network for face perception during the resting state. *Neuroscience letters*, *454*(1), 1-5.

Zhen, Z., Fang, H., & Liu, J. (2013). The Hierarchical Brain Network for Face Recognition. *PLoS ONE*. https://doi.org/10.1371/journal.pone.0059886

Zhu, Q., Zhang, J., Luo, Y. L., Dilks, D. D., & Liu, J. (2011). Resting-state neural activity across face-selective cortical regions is behaviorally relevant. *Journal of Neuroscience*, *31*(28), 10323-10330.