ATYPICAL LATERALIZATION OF LANGUAGE AND FACE PROCESSING IN AUTISM SPECTRUM DISORDER

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Abstract

Autism spectrum disorder (ASD) is characterized by persistent deficits in communication and social interaction, as well as repetitive behaviours and restricted interests. Language and face processing are areas of domain-specific dysfunction impacting social interaction in ASD. Brain function associated with these cognitive domains is typically lateralized across the cerebral hemispheres, such that language and face processing are dominant within the left and right hemispheres, respectively. Furthermore, the degree of lateralization is related to behavioural proficiency in both domains. Converging evidence suggests that the development of lateralization in these separate domains is typically interrelated. Neuroimaging literature demonstrates reduced leftward lateralization of language in ASD, but the existing literature on face processing is inconsistent. Mixed findings are partly due to discrepancies in how regions of interest (ROIs) are localized for neuroimaging analyses. The present work aims to test the hypothesis that ASD is related to atypical lateralization of both language and face processing. First, a quantitative fMRI meta-analysis was conducted to resolve inconsistencies in the literature by identifying the most reliable, concordant patterns of differences in language and face processing in the brain associated with ASD across previous fMRI studies. The findings of the meta-analysis were then used to inform a rigorous analysis of category-related brain activation using individually localized ROIs and task-related fMRI data. However, the question remains regarding whether brain activation differences demonstrate a sustained, fundamental difference in the way

language and faces are processed in the brain, rather than reflecting moment-to-moment differences in attention to these stimuli, motivating the final analysis of intrinsic functional connectivity between category-related brain regions. The findings from the meta-analysis, task-related fMRI analyses, and RSFC analysis of intrinsic functional connectivity converged, demonstrating that ASD is indeed related to reduced functional specialization and hemispheric lateralization of both language and face processing, particularly in posterior lateral temporal cortex. This is an important contribution to the mixed existing literature, and further demonstrates the importance of individual ROI localization when studying neurodiverse populations. Atypical development of hemispheric asymmetry for language and face processing in posterior lateral temporal cortex might be a fundamental factor underlying the behavioural presentation of ASD.

Dedication

To my littlest loves: Joan Harris and Vash the Stampede.

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List of Abbreviations

ACC	Anterior cingulate cortex
ADOS	Autism Diagnostic Observation Schedule
AMG	Amygdala
ATL	Anterior temporal lobe
ASD	Autism spectrum disorder
BOLD	Blood-oxygen-level-dependent
BROC	Broca's area
DSI	Diffusion spectrum imaging
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTI	Diffusion tensor imaging
EEG	Electroencephalography
FFA	Fusiform face area
fMRI	Functional magnetic resonance imaging
fNIRS	Functional near-infrared spectroscopy
FOV	Field of view
FWHM	Full-width-at-half-maximum
IFJ	Inferior frontal junction
IQ	Intelligence quotient
LV	Latent variable
LOC	Lateral occipital complex
MPRAGE	Magnetization prepared rapid acquisition gradient echo

MDS	Multidimensional scaling
NIBS	Non-invasive brain stimulation
OFA	Occipital face area
OPA	Occipital place area
PCG	Precentral gyrus
PET	Positron emission tomography
pFS	Posterior fusiform sulcus
PLS	Partial least squares
PPA	Parahippocampal place area
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
pSTS	Posterior superior temporal sulcus
pVWFA	Posterior visual word form area
RDM	Representational dissimilarity matrix
ROI(s)	Region(s) of interest
RSA	Representational similarity analysis
RSFC	Resting-state functional connectivity
RVT	Respiration volume per time
SDM	Seed-based differential mapping
STS	Superior temporal sulcus
TD	Typically developing
V5	Middle temporal visual area

VWFA	Visual word form area
WERN	Wernicke’s area
WoS	Web of Science
WSS	Within-cluster sum of squares

CHAPTER 1:

General Introduction

1.1 Autism and Terminology

Autism spectrum disorder (ASD) is characterized by persistent deficits in communication and social interaction, as well as repetitive behaviours and restricted interests (American Psychiatric Association, 2013). Many autistic individuals are deservedly proud of their atypical abilities, while others experience significant challenges and cannot live independently (Farley et al., 2009).

Terminology is a sensitive topic with real-world ramifications for vulnerable groups and is thus important to consider (Cascio et al., 2021). Scientists often refer to autistic individuals as those “with ASD” in order to convey that a person is not defined by a diagnosis. The counterargument to this practice is that neurodivergence is not a negative label to be avoided, and further that neurodivergent conditions significantly impact a person’s identity (Botha et al., 2021; Kenny et al., 2016). Hence, the present work refers to the group of people being studied as autistic or ASD participants in order to use more empowering and inclusive terminology (i.e., identity-first, rather than person-first, language).

1.2 Face Processing

The clinical presentation of ASD suggests that neural processing differences are domain-specific, or localized to certain brain networks, rather than a more general abnormality (Dichter, 2012). Preserved domains of function, such as visuospatial skill and rote memory, exist amidst other deficits, such as social

ability (Happé, 1999). Social interaction deficits include avoidance of eye contact, difficulty with emotional regulation, and an impaired ability to understand the emotions of others (American Psychiatric Association, 2013). Faces provide a wealth of vital social information, including identity, age, gender, mood, and gaze direction. Face processing may be an area of domain specific dysfunction that impacts social interaction in ASD (Nomi & Uddin, 2015b; Webb et al., 2017). As such, there is a rich, albeit mixed, literature on face processing in ASD.

Autistic individuals show several behavioural deficits in face processing (Tang et al., 2015), including decreased face memory (Dwyer et al., 2019; Snow et al., 2011; Weigelt et al., 2012) and impaired emotion recognition (Uljarevic & Hamilton, 2013; Wallace et al., 2011). Eye-tracking studies demonstrate reduced attention to social stimuli in ASD participants, as well as altered attention to images of faces, with less time spent looking at the eyes (Åsberg Johnels et al., 2017; Chita-Tegmark, 2016; Guillon et al., 2014, 2016; Kliemann et al., 2010; Noris et al., 2012; Zürcher et al., 2013). Face processing deficits are an early emerging feature in ASD, evident within the first six months of life (Jones et al., 2016). Preferential attention to faces is well documented in typically developing (TD) infants (Johnson, 2005; Johnson et al., 2015). Early face preference may be the result of an adaptive attention bias that promotes the development of social and communication skills (Gliga & Csibra, 2007). An early disruption of face processing could have a cascading effect on neurodevelopment, which could purportedly be a factor underlying the neural basis of ASD (Schultz, 2005).

A general lack of neural responsiveness to social stimuli may not explain brain activation differences in ASD. Rather, autistic people may be utilizing aberrant face processing strategies that are expressed in abnormal brain activation patterns. Intact behavioural performance with abnormal neural activation has been observed in ASD (Harms et al., 2010; Wang et al., 2004), which is suggestive of compensatory mechanisms (Belmonte & Yurgelun-Todd, 2003). ASD groups outperform TD groups in tasks with inverted faces, which further indicates a different underlying mechanism (Bookheimer et al., 2008). Autistic individuals may employ atypical face processing strategies, such as feature-based recognition, more akin to typical object processing systems (Hubl et al., 2003; Scherf, 2010). Further, research indicates that face perception deficits in ASD could be related to a more general bias for local rather than configural processing of objects, since faces are known to be typically processed according to their configuration rather than separately processing individual features (Behrmann et al., 2006).

The neural correlates of face processing have been studied extensively in TD populations (Behrmann et al., 2016; Freiwald et al., 2016; Haist & Anzures, 2017). Functional magnetic resonance imaging (fMRI) reveals a network of connected brain regions involved in the visual processing of faces. Core regions of this network include the “fusiform face area” (FFA; Kanwisher et al., 1997) in the lateral mid-fusiform gyrus, the “occipital face area” (OFA; Gauthier et al., 2000) in the inferior occipital gyrus, and the posterior superior temporal sulcus (pSTS; Puce et al., 1998). The FFA and OFA are implicated in facial recognition and

identification (Ishai et al., 2005; Rossion, Schiltz, et al., 2003; Steeves et al., 2006), while the pSTS is associated with the perception of dynamic aspects of faces, such as gaze direction, lip movement, and facial expressions (Haxby et al., 2000). The so-called extended face network includes the amygdala (AMG) and inferior frontal junction (IFJ), which are important for emotion recognition (Haxby et al., 2000), and the anterior temporal lobe (ATL), which is implicated in memory for facial identity and semantic or bibliographical information associated with faces (Collins & Olson, 2014).

Neuroimaging studies of ASD have demonstrated abnormal activation patterns in response to faces, including decreased amplitude activity in the FFA (Hubl et al., 2003; Pierce, 2001; Schultz et al., 2000; Whyte et al., 2016). Reduced FFA activity has been related to impairments in facial affect processing (Corbett et al., 2009; Wang et al., 2004) and individual face discrimination (Jiang et al., 2013), as well as decreased time spent fixating the eyes in images of faces (Dalton et al., 2005, 2008). Decreased activation for faces has also been shown in the OFA (Humphreys et al., 2008; Scherf, 2010) and amygdala (Corbett et al., 2009; Dalton et al., 2008; Pierce, 2001). Electroencephalography (EEG) has further demonstrated typical neural responses for generic face categorization, but reduced responses for individual face discrimination over occipito-temporal cortex (Vettori et al., 2019).

The pSTS is an area of particular interest, as evidence shows that it is structurally and functionally altered in ASD (Boddaert et al., 2004; Kaiser et al.,

2010; Kana et al., 2014; Levitt, 2003; Paakki et al., 2010; Pelphrey et al., 2011; Saitovitch et al., 2012; Shih et al., 2011). Studies have shown hypoactivation of the pSTS and reduced connectivity with social network regions, including the fusiform gyrus, orbitofrontal cortex, and amygdala (Abrams et al., 2013; Alaerts et al., 2014, 2015; Hadjikhani et al., 2007; Lai et al., 2010; Pierce et al., 2004; Weisberg et al., 2014). Studies have also shown that pSTS activity predicts autism spectrum traits in TD individuals (Hasegawa et al., 2013; Nummenmaa et al., 2012; von dem Hagen et al., 2011). The pSTS is critical for processing dynamic faces, facial expressions, multisensory integration, biological motion, and theory of mind, which are all cognitive functions that may be impacted in ASD (Frith, 2001; Koldewyn et al., 2011; Yang et al., 2015).

Several fMRI studies of ASD have reported divergent results, such as no differences in FFA activation for faces (Hadjikhani et al., 2004, 2007), and no differences in connectivity patterns of face processing regions in ASD compared to TD populations (Noonan et al., 2009; Redcay et al., 2013). These inconsistencies in the fMRI literature on face processing in ASD warrant further rigorous investigation.

1.3 Language

Language impairments are commonly considered a “hallmark feature” of ASD (Herringshaw et al., 2016). In fact, language decrements were previously a

diagnostic requirement for ASD in the 4th Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 2000). However, this requirement has been eliminated as of the DSM-5 (American Psychiatric Association, 2013).

Autistic language ability can range from completely non-verbal to idiosyncratic with unusual prosody or echolalia. Articulation, vocabulary, and grammatical skills are often intact, while difficulties with prosody and abstract use of language are common (Mody & Belliveau, 2013). Both expressive and receptive language impairments are closely related to social deficits. Differences in communication are evident preverbally, as autistic infants use fewer symbolic gestures like pointing (Mody & Belliveau, 2013). Rapid auditory, but not visual, processing is diminished in autism, and this temporal processing deficit is further related to language decrements (Foss-Feig et al., 2017). Early language ability and childhood IQ are the strongest observed predictors of later outcome, but with sizeable individual differences (Magiati et al., 2014).

Notably, autistic peer-to-peer information transfer is as effective as among groups of non-autistic peers. However, mixed groups of autistic and non-autistic adults experience reduced retention of details and reduced interpersonal rapport (Crompton et al., 2020). While perceptual categorization is generally intact in ASD, the internal organization of perceptual categories may differ, leading to challenges in communicating effectively (Mercado et al., 2020).

Neuropsychology and neuroimaging demonstrate that the TD language system consists of a network of connected areas in perisylvian cortex (Catani et al., 2005). Core language regions include Broca's area for speech production (Broca, 1861) in the left pars opercularis of the inferior frontal gyrus, and Wernicke's area for speech comprehension (Wernicke, 1874) in the left planum temporale, posterior to Heschl's gyrus within posterior superior lateral temporal cortex (Price, 2010). The extended language network further includes a premotor area in the left precentral gyrus (PCG; Alexander et al., 1990; Ferstl et al., 2008). In literate individuals, the language network extends to include the "visual word form area" (VWFA; Cohen et al., 2000) in left ventral occipitotemporal cortex, which becomes specialized for reading as people become proficient in the skill (Dehaene & Cohen, 2011). Notably, functional connectivity strength between the VWFA and Wernicke's area is predictive of semantic classification performance with words, but not other stimulus categories, in TD participants (Stevens et al., 2017). Literate individuals also show word-related activation in an occipital region termed the posterior VWFA (pVWFA; Dehaene & Cohen, 2011).

Structural MRI studies have found differences in the relationship between cortical thickness and language scores in ASD and TD groups (Crutcher et al., 2018). Functional neuroimaging studies of language processing have also found abnormalities in ASD, including recruitment of regions not typically associated with language (Eyler et al., 2012; Gervais et al., 2004; Groen et al., 2010; Kana et al., 2006; Kana & Wadsworth, 2012; Mizuno et al., 2011). However, many studies

report generally intact language comprehension in individuals with ASD when the language tasks involve visual components (Kamio & Toichi, 2000; Sahyoun et al., 2009, 2010). One structural equation modeling study of intrinsic functional connectivity found that a right extrastriate cortex visual region was a core component of the language network in ASD but not TD individuals (Shen et al., 2012). Atypical recruitment of visual regions during language processing may reflect a compensatory mechanism accounting for the lack of performance decrements when language tasks have a visual component.

A commonly reported finding in neuroimaging studies of language in autism is a reduction of the typically observed left hemisphere lateralization of this cognitive process (Herringshaw et al., 2016; Joseph et al., 2014; Jouravlev et al., 2020; Kleinhans et al., 2008; Knaus et al., 2010; Lindell & Hudry, 2013), which is described in detail in the following section.

1.4 Hemispheric Lateralization

Lateralization is an important aspect of neural specialization among vertebrates, whereby distinct cortical areas become specialized for different components of perception and action asymmetrically across the two cerebral hemispheres (Rentería, 2012; Vallortigara & Rogers, 2005). Lateralization is related to handedness, whereby most right-handers show language preference in

the left hemisphere, and preference for visuospatial functions in the right hemisphere (Mesulam, 1990).

Interestingly, functional lateralization is also observed in the everyday behaviour of various species in their natural environments (Vallortigara & Rogers, 2005). For instance, toads are more likely to jump away from predators seen in their left compared to their right visual field, suggesting a right hemisphere preference for reacting to predators (Lippolis et al., 2002), and more likely to strike at prey seen in their right compared to their left visual field, suggesting a left hemisphere preference for reacting to prey (Vallortigara et al., 1998). Functional lateralization likely reflects enhanced efficiency of the brain and enhanced cognitive capacity in humans. However, the aligned direction of functional asymmetries across the majority of individuals in populations may arise as an evolutionarily stable method of coordinating behaviour among individuals (Vallortigara & Rogers, 2005).

The typically observed leftward lateralization of language and rightward lateralization of face processing were first discovered through the study of neuropsychology patients with selective brain damage localized to either the left or right hemisphere, who showed selective impairments in language or face processing, respectively (Broca, 1861; Whiteley & Warrington, 1977). Neuroimaging further demonstrates right hemisphere dominance for face processing, and left hemisphere dominance for language, in TD individuals (Cohen et al., 2002; Meng et al., 2012; Rossion, Joyce, et al., 2003). Moreover, the level

of lateralization is correlated with behavioural performance in both domains (Hirnstein et al., 2010). Neuroimaging also suggests that two distinct forms of functional lateralization exist across the hemispheres, where the left hemisphere interacts more exclusively with itself, and the right hemisphere interacts in a more integrative manner with both hemispheres (Gotts, Jo, et al., 2013).

Interesting evidence suggests that the development of face and language lateralization is interrelated (Behrmann & Plaut, 2013, 2014; Plaut & Behrmann, 2011). As both words and faces require high-acuity visual processing, it has been proposed that they compete for representational space adjacent to retinotopic cortical areas that encode foveal vision (Hasson et al., 2002; Levy et al., 2001; Plaut & Behrmann, 2011). In order to maximize efficiency and minimize signal propagation distance, orthographic representations move proximally toward left lateralized language areas, and thus come to rely upon the VWFA in left ventral occipitotemporal cortex as an intermediate cortical region bridging early visual and language areas (Behrmann & Plaut, 2020). Consequently, as the VWFA becomes increasingly specialized for processing orthographic stimuli, face processing becomes displaced to the right ventral occipitotemporal cortex (Behrmann & Plaut, 2020; Dundas et al., 2013; Plaut & Behrmann, 2011). This theory is supported by neuroimaging evidence from young children, where left hemisphere activation in response to faces decreases in proportion to increasing orthographic knowledge (Cantlon et al., 2011). Illiterate adults also demonstrate increased left hemisphere activation for faces when compared to literate adults, irrespective of whether

literacy was acquired during childhood or adulthood (Dehaene et al., 2010). This is aligned with the neuronal recycling hypothesis, which posits that cultural domains whose invention are too recent to have impacted human evolution, such as reading and arithmetic, rely on evolutionarily older brain circuits and inherit many of their structural constraints (Dehaene & Cohen, 2007).

There is also research suggesting that low-level perceptual deficits in multisensory integration could underlie the downstream higher order language and social impairments in ASD (Bahrick & Todd, 2012; Stevenson et al., 2014). Notably, regions within posterior lateral temporal cortex (for instance, the pSTS) in both the left and right hemispheres are critically involved in multisensory integration (Beauchamp et al., 2004; Stevenson & James, 2009), and play important roles in language and face processing, respectively (Redcay, 2008).

A relatively large neuroimaging literature demonstrates a deficit in the leftward lateralization of language processing that is correlated with language impairment in ASD (Herringshaw et al., 2016; Joseph et al., 2014; Jouravlev et al., 2020; Kleinhans et al., 2008; Knaus et al., 2010; Lindell & Hudry, 2013). Reduced hemispheric asymmetry of cortical thickness has also been demonstrated in medial frontal, orbitofrontal, cingulate, and inferior temporal areas (Postema et al., 2019). However, there is a lack of fMRI studies that focus on the rightward lateralization of face processing in ASD. EEG, magnetoencephalography (MEG), and functional near-infrared spectroscopy (fNIRS) indeed show decreased right hemisphere specialization for faces (Bailey et al., 2005; Dawson et al., 2005; Jung

et al., 2016; Keehn et al., 2015; Luckhardt et al., 2017). Diffusion tensor imaging (DTI) and diffusion spectrum imaging (DSI) tractography also demonstrate reduced hemispheric asymmetry of anatomical white matter microstructure in ASD (Carper et al., 2016; Lo et al., 2011). Behavioural and eye-tracking studies further indicate a deficit in the rightward lateralization of face processing. For instance, ASD participants show improved task performance with high rather than low spatial frequency face stimuli (Deruelle et al., 2004), where the left and right hemispheres are thought to preferentially process high and low spatial frequencies, respectively. Also, ASD participants show a lack of the typically observed left visual field bias for processing faces (Dundas et al., 2012), where the right occipital cortex is known to process the left visual field and vice versa. While converging evidence suggests that ASD is related to reduced rightward lateralization of face processing, there is a scarcity of fMRI studies making this claim.

1.5 Resting-State fMRI

Classical fMRI research focuses on correlating small changes in the amplitude of blood-oxygen-level-dependent (BOLD) signal with explicit experimental conditions. Resting-state functional connectivity (RSFC) analysis of spontaneous fluctuations in BOLD signal demonstrates that brain regions that are coactive during tasks tend to also have correlated low frequency BOLD signal during rest (Fox & Raichle, 2007). Some researchers posit that the statistical

histories of co-activation between neurons shape functional connectivity relationships via Hebbian mechanisms (Fair et al., 2007; Stevens & Spreng, 2014). Consistent with this hypothesis, practice-induced changes in RSFC that correlate with behavioural performance have been observed between task-involved regions after category-related task performance (Stevens et al., 2010), associative encoding (Tambini et al., 2010), motor learning (Vahdat et al., 2011), visual perceptual learning (Lewis et al., 2009), multisensory perceptual learning (Powers et al., 2012), and reasoning training (Mackey et al., 2013).

RSFC is associated with individual differences in various cognitive domains and reveals dynamic processes that are actively involved in cognition, rather than reflecting passive or epiphenomenal activity (Stevens & Spreng, 2014). Notably, RSFC work demonstrates that the functional organization of category-related cortical areas is constrained by privileged functional connectivity with other brain regions that process category-relevant properties (Stevens et al., 2015). RSFC is related to anatomical connectivity (Fox & Raichle, 2007), and it is methodologically advantageous as it provides information about intrinsic neural properties and circumvents some limitations of task-based fMRI, such as developing common paradigms for testing the brain's functional systems without the constraints of *a priori* hypotheses (Biswal et al., 2010; Buckner et al., 2013; Fox et al., 2005; Kelly et al., 2012).

Research demonstrates that decreased functional connectivity in ASD is most pronounced in regions of the social brain, especially between limbic regions

involved in affective processing and language-related regions (Gotts et al., 2012). ASD research further indicates decreased connectivity of the default network (Washington et al., 2014; Weng et al., 2010), which is an intrinsic brain network that supports internally focused cognition (Spreng et al., 2010). Other work indicates hyperconnectivity of the salience network that is related to sensory over-responsivity in ASD (Green et al., 2016). RSFC work also demonstrates increased connectivity between primary sensory and subcortical regions (Cerliani et al., 2015). Some RSFC studies suggest that autistic brains show increased local connectivity and decreased global connectivity in social and sensory brain networks (Courchesne & Pierce, 2005; Dajani & Uddin, 2016). However, findings across studies are mixed, and fMRI measures of local connectivity may be especially susceptible to site and cohort variability, including whether the eyes are open or closed during rest (Hull et al., 2017; Nair et al., 2018).

1.6 Individual Localization

As a spectrum of disorders, autism is notably heterogeneous, complicating its investigation (Chahrour et al., 2016; Geschwind & Levitt, 2007). Further, heterogeneity in scientific methodology has led to a mixed and sometimes conflicting literature on the subject (Dichter, 2012; Müller et al., 2011; Vissers et al., 2012). Methodological rigor is imperative to understanding the neurological differences between ASD and TD individuals.

Autistic people present a wide range of individual differences that contribute to divergent results in the literature (Geschwind & Levitt, 2007; Pierce, 2001). Group averaged data require cautious interpretation in neurodiverse populations. Discrepancies in the literature could be due to methodological differences in identifying regions of interest (ROIs) for fMRI analysis. Standard ROI identification methods, namely, normalization to a common brain atlas space (e.g., Talairach, MNI) and atlas definitions, significantly impact the results of fMRI analyses (Beisteiner et al., 2010; Stevens et al., 2017). Neuroanatomical experts can identify ROIs with greater consistency and reliability than developed software (Gartus et al., 2007; Zhang et al., 2013). Studies reveal significant errors when relying on atlases to define ROIs (Rodionov et al., 2009).

Individual localization of key brain regions is vital to accurately characterizing/quantifying their neural activity. Group-level definitions are not sensitive enough to detect subtle effects in diverse brains. Group-level analyses may not be appropriate in many studies of complex structures (Vandenbroucke et al., 2004). Moreover, outliers and individual differences have a greater impact on group-level analyses as compared to individually localized ROIs (Poldrack, 2007). Individual localization of ROIs may be particularly important in individuals with atypical brain organization (Rodionov et al., 2009; Vandenbroucke et al., 2004).

ROI location significantly impacts the results in fMRI studies of ASD. Findings of abnormal activation patterns or reduced connectivity between brain regions may be due to varying ROI identification techniques. When applying ROI

coordinates from TD groups to autistic individuals, underconnectivity findings can result simply from variability in ROI location (Müller et al., 2011). More precise localization of regions in fMRI analysis can account for inter-subject variability and mitigate the influence of previous assumptions. For instance, differences between ASD and TD brain activation during verbal and visuospatial tasks have been demonstrated at the individual level, while no differences were evident at the group level (Strandberg et al., 2011). Identifying ROIs using individual functional localizers in each participant's native space, rather than using anatomically derived ROIs or group averages in standardized space, obtains more precise results regarding brain network activity (e.g., Glezer & Riesenhuber, 2013; Stevens et al., 2017). Observed differences in individually localized ROIs can be more confidently attributed to differences in ROI activation and connectivity, rather than a possible measurement bias towards TD populations.

1.7 Current Objective

The present dissertation aims to test the general hypotheses that ASD is related to reduced hemispheric specialization of both language and face processing compared to TD populations, and that functional abnormalities within posterior lateral temporal cortex in particular are associated with ASD. This investigation begins with a quantitative fMRI meta-analysis (Chapter 2) in order to situate the research question within the broader context of the existing literature,

and to determine what findings are consistent across studies in the mixed neuroimaging literature on face processing in ASD. Importantly, Chapter 2 comprises the first quantitative fMRI meta-analysis of its kind to directly compare studies of both language and face processing in ASD. Next, Chapter 3 outlines the General Methods used in the following two chapters, which examine the hemispheric lateralization of language and face processing in terms of task-related brain activation (Chapter 4) and intrinsic functional connectivity (Chapter 5) in matched groups of high-functioning ASD and TD participants. These chapters comprise hypothesis-driven univariate and data-driven multivariate fMRI analyses.

The order of these chapters is important. First, the fMRI meta-analysis is necessary to resolve inconsistencies in the mixed existing literature, and inform the rigorous analysis of category-related brain activation using individually localized ROIs. However, the question would remain regarding whether brain activation differences demonstrate a sustained, fundamental difference in the way language and faces are processed in the brain, rather than reflecting moment-to-moment differences in attention to these stimuli, motivating the analysis of intrinsic functional connectivity. Finally, Chapter 6 brings all the present work together into a cohesive story in the General Discussion.

CHAPTER 2:

Quantitative fMRI Meta-Analysis[1]

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2.1 Abstract

Autism is characterized by difficulties in communication and social interaction, which have been reflected in atypical processing of language and faces in the brain. While these may be separate and unrelated domains of cognitive impairment, some evidence suggests that they may be interrelated. Here, we report the first quantitative meta-analysis of functional MRI studies on both language and face processing in ASD [36 articles on language comprising 599 ASD and 620 typically developing (TD) participants; 28 articles on face processing comprising 437 ASD and 470 TD participants]. This work extends previous meta-analyses, which investigated either language or face processing only, by performing cross-domain analyses to investigate the relationship between these cognitive domains in the context of ASD. Results of the present meta-analysis demonstrate that ASD is related to atypical hemispheric specialization of both language and face processing, which is particularly prominent in the superior temporal sulcus in both hemispheres.

2.2 Introduction

ASD has been characterized by difficulties in communication and social interaction, as well as restricted and repetitive behaviours (American Psychiatric Association, 2013). Two of the most widespread and consistent findings in the clinical literature have been abnormalities in the processing of language (Siegal & Blades, 2003) and faces (Nomi & Uddin, 2015a). While these have typically been considered separate and unrelated domains of cognitive impairment, evidence from several lines of research suggests that they might be interrelated. First, research has demonstrated intriguing links between the left and right hemispheric specialization of language and face processing, respectively, in neurotypical development (Behrmann & Plaut, 2013, 2014, 2020; Dundas et al., 2013; Plaut & Behrmann, 2011). There has also been research suggesting that low-level perceptual deficits in multisensory integration underlie the downstream higher order language and social impairments in ASD (Bahrick & Todd, 2012; Stevenson et al., 2014). Notably, regions within posterior lateral temporal cortex (e.g., posterior superior temporal sulcus: pSTS) in both the left and right hemispheres are critically involved in multisensory integration (Beauchamp et al., 2004; Stevenson & James, 2009), and play important roles in language and face processing, respectively (Redcay, 2008). Finally, research has shown that decreased functional connectivity in ASD is most pronounced in regions of the social brain, especially between limbic regions involved in affective processing and language-related regions (Gotts et al., 2012).

Individual neuroimaging studies of the neural correlates of atypical language and face processing in ASD have reported disparate findings, due in large part to substantial variability in methodology and the kind of processing engaged by different tasks across studies. Given a sufficient number of empirical studies, quantitative meta-analyses of neuroimaging findings can identify the most concordant reliable group differences across multiple studies. Though findings have been mixed, there is convergent evidence across several neuroimaging studies supporting the hypothesis that communication deficits in ASD are associated with reduced hemispheric lateralization of language processing (Jouravlev et al., 2020; Kleinhans et al., 2008; Knaus et al., 2010). This hypothesis was supported by a quantitative meta-analysis demonstrating concordant hyperactivation of two regions in the right hemisphere, and hypoactivation in several regions in the left hemisphere, involved in language processing (Herringshaw et al., 2016). However, the number of previous studies eligible for meta-analysis at the time was near the recommended minimum required to reliably detect smaller effects and avoid effects being driven by single experiments (Eickhoff et al., 2016).

Despite reliable differences in behavioral measures of face processing in ASD (Weigelt et al., 2012), neuroimaging studies of neural differences in ASD have reported even more disparate findings. For example, some studies have reported differences in face-related activation of the critically important “fusiform face area” (FFA) in ASD (Corbett et al., 2009; Jiang et al., 2013; Pierce, 2001; Schultz et al.,

2000; Wang et al., 2004; Weisberg et al., 2014), while others found no significant differences in this region (Hadjikhani et al., 2004, 2007). Interestingly, studies have reported aberrant neural activation (Hadjikhani et al., 2007) and connectivity (Weisberg et al., 2014) of the right pSTS associated with face processing in ASD. A quantitative meta-analysis of fMRI studies of face processing in ASD found concordant differences in only one small region within the left fusiform gyrus, which showed reduced face-related activation in ASD (Nickl-Jockschat et al., 2015); however, the number of eligible studies available at the time was below the recommended minimum for reliable quantitative meta-analysis.

The quantitative fMRI meta-analysis reported here expands upon the two aforementioned prior meta-analyses on language (Herringshaw et al., 2016) and face processing (Nickl-Jockschat et al., 2015) in ASD by 1) including more recently published articles over the ensuing 7-9 years since the prior searches were conducted, and 2) analyzing language and face processing simultaneously and performing cross-domain analyses to explore the relationship between these cognitive domains in the context of ASD. The goal of this study was to directly compare concordant differences in language and face processing in ASD relative to typically developing (TD) controls across studies, in order to investigate the hypotheses that ASD is associated with reduced hemispheric functional specialization of these cognitive domains, and that functional abnormalities within posterior lateral temporal cortex in particular are associated with ASD.

2.3 Methods

2.3.1 Article and Contrast Selection

Literature searches were performed using PubMed (pubmed.ncbi.nlm.nih.gov) and Web of Science (www.webofknowledge.com) databases, including all papers published until December 31, 2020. For language processing, the following search terms were used: "(autism *OR* ASD) *AND* (language *OR* language processing *OR* semantics *OR* pragmatic *OR* speech) *AND* (fMRI)" (adapted from Herringshaw et al., 2016). The search performed by Herringshaw et al. (2016) included articles published between 1999-2014. Thus, the present search on language processing in ASD screened articles published since 2013 to ensure no potentially eligible papers were missed. Articles from this and another previous meta-analysis on speech perception in ASD (Tryfon et al., 2018) were screened for eligibility before inclusion in the present analysis (Figure 2.1).

For face processing, the following search terms were used: "(autism *AND* face *AND* processing) *OR* (autism *AND* face *AND* processing *AND* fMRI) *OR* (ASD *AND* face *AND* processing) *OR* (ASD *AND* face *AND* processing *AND* fMRI) *OR* (autism *AND* face *AND* fMRI) *OR* (ASD *AND* face *AND* fMRI)" (adapted from Nickl-Jockschat et al., 2015). The search performed by Nickl-Jockschat et al. (2015) included articles published between 2001-2012. Thus, the present search on face processing in ASD screened articles published since 2011 to ensure that no potentially eligible papers were missed (Figure 2.2).

Articles deemed eligible followed the standard exclusion protocol for fMRI meta-analysis (Müller et al., 2018). This method deemed articles eligible based on the following criteria: (1) original peer reviewed fMRI study published in English; (2) whole-brain analysis not restricted to regions of interest, with results thresholded consistently across the whole brain; (3) results reported in standard stereotactic coordinates (i.e., Talairach or MNI); (4) included both an ASD group diagnosed with standard clinical protocols and a TD control group; and (5) only unique participants included in each article. Additionally, all participants were awake during fMRI scanning, and children under 4 years old were not included. Lastly, for any articles containing both face and language stimuli in the study, only activation/contrasts associated with one of these domains (i.e., either face or language, but not both) were included in our analyses, in order to reduce interdependence between face and language processing (e.g., 'faces > letters' would be deemed an ineligible contrast).

Of the 32 unique articles included in two previous meta-analyses on language processing in ASD (Herringshaw et al., 2016; Tryfon et al., 2018), 27 articles met the present eligibility criteria. An additional 9 articles were deemed eligible, bringing the total to 36 studies (Tables 2.1 and 2.3). All 14 articles included in the previous meta-analysis on face processing in ASD (Nickl-Jockschat et al., 2015) met the present eligibility criteria (Müller et al., 2018) and were included in the current analyses. Using the same eligibility criteria, an additional 14 articles were included, totaling 28 studies on face processing (Tables 2.2 and 2.4).

In total, language articles (Figure 2.1) comprised 599 ASD participants [age grand mean (SD) = 19.67 (7.40), range in mean ages = 9.66–36 years] and 620 TD participants [age grand mean (SD) = 19.71 (7.59), range in mean ages = 10.40–34 years]. Face articles (Figure 2.2) comprised 437 ASD participants [age grand mean (SD) = 20.80 (7.87), range in mean ages = 10.51–37 years] and 470 TD participants [age grand mean (SD) = 20.15 (7.20), range in mean ages = 9.72–35.30 years]. The number of participants and number of foci included in each individual analysis (i.e., between-group and within-group contrasts) have been outlined in Figures 2.1 and 2.2.

2.3.2 Software and Analysis

Analyses were performed using seed-based differential mapping (SDM) software developed by the SDM Project (www.sdmproject.com/). SDM is a coordinate-based method that calculates the above-chance convergence of foci reported across different experiments (Albajes-Eizagirre & Radua, 2018). SDM creates statistical brain maps of effect-sizes and corresponding variances from reported peak coordinates and *t*-statistics (Albajes-Eizagirre et al., 2019). To optimally balance sensitivity and specificity of the analysis, the recommended statistical thresholding parameters were used: the full-width-at-half-maximum (FWHM) of the unnormalized Gaussian smoothing kernel was set at 20 mm and the resulting statistical maps were thresholded at $P < 0.005$ uncorrected for multiple comparisons, which has been demonstrated to be approximately

equivalent to a corrected $P < .05$, with a peak height threshold of SDM-$Z > 1$ (Radua et al., 2012). Clusters containing at least 10 voxels were considered relevant for further discussion. All reported voxels were 2 x 2 x 2 mm in size.

Foci reported from between-group contrasts (i.e., ASD>TD and TD>ASD) were examined in each cognitive domain (i.e., language and face processing) separately to assess whether ASD is associated with reduced leftward lateralization of language and/or reduced rightward lateralization of face processing. Potential overlap of brain regions showing group differences in both domains was examined to determine if group differences in language and face processing are related to any common brain regions. Of particular interest were any potential regions showing a crossover double dissociation – i.e., hypoactivation for one domain and hyperactivation for the other in one hemisphere (e.g., a region in the left hemisphere showing both decreased language-related activation and increased face-related activation) and/or vice versa in the other hemisphere (e.g., a region in the right hemisphere showing both decreased face-related activation and increased language-related activation).

Foci reported from within-group contrasts (i.e., ASD only and TD only) were examined with conjunction (i.e., concordant foci reported in both groups) and contrast (i.e., concordant foci reported in one group but not the other) analyses, in order to investigate commonalities and differences, respectively, across groups within each cognitive domain. Within-group contrasts were further examined in conjunction analyses across domains (i.e., foci reliably reported in both face and

language domains) in each group separately, to test our hypothesis that ASD is associated with reduced domain-related specialization of brain regions involved in language and face processing.

2.4 Results

2.4.1 Between-Group Contrasts

Clusters within the following regions were associated with reduced language-related activation in ASD relative to TD groups (Table 2.5; Figure 2.3): left inferior frontal and middle temporal gyri (3059 voxels, SDM-Z = -2.26, P < .0001), bilateral anterior cingulate/paracingulate (1010 voxels, SDM-Z = -1.73, P = .0001), right middle temporal gyrus (61 voxels, SDM-Z = -1.23, P = .0025), and left occipital temporal sulcus (13 voxels, SDM-Z = -1.17, P = .0035). Clusters within the following regions were associated with increased language-related activation in ASD relative to TD groups: right middle temporal gyrus (258 voxels, SDM-Z = 1.66, P = .0002), right cuneus/precuneus (179 voxels, SDM-Z = 1.39, P = .0011), right medial cingulate/paracingulate (104 voxels, SDM-Z = 1.28, P = .0022), and right supramarginal gyrus (54 voxels, SDM-Z = 1.28, P = .0023). Notably, all clusters associated with increased language-related activation in the ASD group relative to the TD group were located within the right hemisphere.

Clusters within the following regions were associated with decreased face-related activation in ASD relative to TD groups (Table 2.5; Figure 2.3): right

fusiform gyrus extending into the cerebellum (2536 voxels, SDM-*Z* = -2.63, *P* < .0001), left calcarine fissure (745 voxels, SDM-*Z* = -1.81, *P* = .0002), left amygdala and insula (632 voxels, SDM-*Z* = -1.94, *P* = .0001), right inferior occipital gyrus (407 voxels, SDM-*Z* = -1.63, *P* = .0005), and left fusiform gyrus (75 voxels, SDM-*Z* = -1.36, *P* = .0024). Clusters within the following regions were associated with increased face-related activation in ASD relative to TD groups: left middle occipital gyrus (748 voxels, SDM-*Z* = 1.91, *P* = .0002), bilateral anterior cingulate (122 voxels, SDM-*Z* = 1.27, *P* = .0027), left striatum (105 voxels, SDM-*Z* = 1.26, *P* = .0028), left middle temporal gyrus (82 voxels, SDM-*Z* = 1.17, *P* = .0036), and right middle frontal gyrus (42 voxels, SDM-*Z* = 1.15, *P* = .0038).

Overlaying the between-group SDM maps across group and domain to search for potential regions showing a crossover double dissociation (i.e., ASD>TD for language processing and TD>ASD for face processing in one hemisphere; and ASD>TD for face processing and TD>ASD for language processing in the other) revealed the following areas of overlap (Table 2.6; Figure 2.3): 1) One region within the right superior temporal sulcus (STS; 110 voxels) was associated with greater face-related activation in TD relative to ASD groups (SDM-*Z* = -1.63, *P* = .0005), and conversely, greater language-related activation in ASD relative to TD groups (SDM-*Z* = 1.66, *P* = .0002); 2) Two regions showed the opposite double dissociation: the left STS (58 voxels) and right anterior cingulate cortex (ACC; 29 voxels) showed greater language-related activation in TD relative to ASD groups (left STS: SDM-*Z* = -2.26, *P* < .0001; right ACC: SDM-*Z* = -1.73, *P* = .0001), and

conversely, greater face-related activation in ASD relative to TD groups (left STS: SDM-Z = 1.17, P = .0036; right ACC: SDM-Z = 1.27, P = .0027). This identified brain regions showing reduced specialization for both language and face processing in ASD, relative to TD groups, most notably including the STS in both the left and right hemispheres, which showed the opposite effects across hemispheres in the predicted directions.

2.4.2 Within-Group Contrasts

For language processing, the conjunction analysis of foci from within-group contrasts revealed three clusters that showed concordant activation in both TD and ASD groups within the following regions: left inferior frontal and lateral temporal gyrus (9085 voxels), bilateral superior frontal gyrus (1673 voxels), and right superior/middle temporal gyrus (1582 voxels) (Table 2.7; Figure 2.4). The contrast analysis of foci from within-group contrasts revealed one large cluster that showed language-related activation in TD>ASD groups within the bilateral superior frontal gyrus (1773 voxels, SDM-Z = -2.80, P < .0001) (Table 2.8; Figure 2.4). This analysis did not reveal any clusters showing the opposite effect – i.e., ASD>TD for language-related activation.

For face processing, the conjunction analysis of foci from within-group contrasts revealed two clusters that showed concordant face-related activation in both TD and ASD groups within the following regions: right (3045 voxels) and left (2046 voxels) fusiform gyri (Table 2.7; Figure 2.4). The latter clusters extended into

the cerebellum bilaterally, especially so in the right hemisphere. The contrast analysis of foci from within-group contrasts revealed three clusters that reliably showed face-related activation in TD>ASD groups within the following regions: right amygdala and insula (598 voxels, SDM-*Z* = -2.00, *P* = .0003), right inferior occipital gyrus (226 voxels, SDM-*Z* = -1.88, *P* = .0006), and right inferior frontal gyrus (31 voxels, SDM-*Z* = -1.52, *P* = .0030) (Table 2.8; Figure 2.4). Notably, these clusters associated with decreased face-related activation in ASD relative to TD groups were all located within the right hemisphere. This analysis did not reveal any clusters showing the opposite effect – i.e., ASD>TD for face-related activation.

The domain conjunction analysis, which examined whether either group showed concordant foci reliably engaged by both language and face processing, revealed no brain regions associated with both cognitive domains in TD groups. However, one region in the right posterior lateral temporal cortex, centered on the right pSTS (119 voxels), was reliably engaged in both language and face processing, concordantly across studies (Table 2.9; Figure 2.4). This demonstrated reduced specialization of this critically important brain region related to both language and face processing in ASD.

2.5 Discussion

Results of the present meta-analysis strongly supported the hypothesis that ASD is associated with reduced specialization of both language and face

processing within left and right hemispheres, respectively. This was especially evident in the language domain, for which all clusters associated with hyperactivation for language in ASD were located within the right hemisphere. These included clusters within the right posterior middle temporal gyrus (258 voxels), right cuneus/precuneus (179 voxels), right medial cingulate (104 voxels), and right supramarginal gyrus (54 voxels). Of these regions, only the posterior middle temporal gyrus has been considered a core language region, but the others have been associated with the extended language network (Braga et al., 2020; Fedorenko & Thompson-Schill, 2014; Ferstl et al., 2008; Friederici, 2011; Poeppel et al., 2012). The only right hemisphere region reliably showing language hypoactivation in ASD was located anteriorly in the right middle temporal gyrus (61 voxels) – a region typically associated with language processing despite its right hemisphere location (Friederici, 2011; Poeppel et al., 2012).

The largest cluster showing hypoactivation for language in ASD was located within the left inferior frontal gyrus, extending back into the left lateral temporal cortex (3059 voxels) – i.e., reliably reduced activation in ASD groups across a large swath of classical language areas in the left hemisphere (Fedorenko & Thompson-Schill, 2014). Another large cluster related to language hypoactivation in ASD was located within bilateral anterior cingulate cortex (1010 voxels) – a region implicated in neurotypical language processing (Braga et al., 2020). There was also a small cluster within the left occipital temporal sulcus (13 voxels) related to language hypoactivation in ASD. This is the purported location of the “visual

word form area" (VWFA; Cohen et al., 2000) – a brain region that is critical for reading (Dehaene & Cohen, 2011). Notably, connectivity strength between the VWFA and Wernicke's area, a core region for language comprehension, has been shown to predict performance on semantic classification of words in TD participants (Stevens et al., 2017).

The conjunction analysis of foci from within-group contrasts demonstrated that both TD and ASD groups showed concordant activation in many areas of the classical language network: a large swath encompassing the left inferior frontal gyrus and left lateral temporal lobe (9085 voxels), a smaller region within the right middle/superior temporal gyrus (1582 voxels), and another swath in bilateral posterior superior frontal gyrus (1673 voxels). Thus, ASD groups showed language activation in much of the core language network (Fedorenko & Thompson-Schill, 2014), but this activation was lower in amplitude relative to TD groups, as indicated by the results from between-group contrasts reported above. The contrast analysis of within-group foci revealed one additional cluster within bilateral superior frontal gyrus (1773 voxels) showing hypoactivation for language in ASD. Thus, both groups showed language-related activation in the superior frontal gyrus, but this activation extended farther anteriorly in TD compared to ASD groups.

Similar to the previous meta-analysis by Herringshaw and colleagues (2016), the present analysis showed that both groups demonstrate largely overlapping language network activation in general. Further in common, both meta-analyses demonstrated hypoactivation in core language areas in ASD,

including regions within the left inferior frontal gyrus, left superior temporal gyrus, and bilateral middle temporal gyri. Whereas the previous meta-analysis suggested that ASD groups show right hemisphere hyperactivation in core language regions (i.e., the right inferior frontal and superior temporal gyri), the present work demonstrated right hemisphere hyperactivation in extended language network regions (i.e., the right precuneus, medial cingulate, and supramarginal gyrus). Importantly, the present meta-analysis corroborated the previous findings that ASD is associated with reduced leftward lateralization of language processing in the brain.

With respect to face processing, the conjunction analysis of foci from within-group contrasts demonstrated that both TD and ASD groups showed concordant face-related activation across large portions of the right (3045 voxels) and left (2046 voxels) fusiform gyri. However, the contrast analysis of within-group foci revealed that ASD groups showed face-related hypoactivation in three right hemisphere regions that have been typically associated with face processing (Haxby et al., 2000): the right amygdala and insula (598 voxels), right inferior occipital and middle temporal gyri (226 voxels), and right inferior frontal gyrus (31 voxels). These findings provided strong support for the hypothesis that ASD is associated with reduced rightward lateralization of face processing.

Further supporting the hypothesis of reduced lateralization in ASD, the largest cluster in the between-group contrasts that showed hypoactivation for face processing in ASD was within the right fusiform gyrus (2536 voxels) –

encompassing the location of the much investigated FFA (Kanwisher et al., 1997). Furthermore, another cluster that showed face-related hypoactivation in ASD was located within the right inferior occipital gyrus (407 voxels), encompassing the location of another core face processing region – the OFA (Gauthier et al., 2000).

The right fusiform cluster of face-related hypoactivation in ASD extended down into the cerebellum. Eight of the 28 included articles on face processing indeed reported cerebellar effects (Critchley et al., 2000; Dapretto et al., 2006; Deeley et al., 2007; Koshino et al., 2008; Okamoto et al., 2017; Pierce et al., 2004; Schulte-Ruther et al., 2011; Zurcher et al., 2013). Interestingly, previous work has demonstrated decreased functional connectivity between a right cerebellar region and the language network in ASD (Verly et al., 2014). Other previous work has also shown decreased connectivity between a left cerebellar region and the right temporoparietal junction, which is an area very close to the pSTS (Igelström et al., 2017). Future empirical research should further investigate the role of the cerebellum in functional connectivity differences observed in ASD.

Face-related hypoactivation in ASD was also found within the left amygdala and insula (632 voxels) and left fusiform gyrus (75 voxels), which have been associated with face processing despite their location in the left hemisphere (Haxby et al., 2000). The previous fMRI meta-analysis on face processing in ASD found only a single cluster of face-related hypoactivation in the left fusiform gyrus (Nickl-Jockschat et al., 2015). A similar left fusiform cluster of hypoactivation was found in the present analysis, among other larger clusters. The finding of more

numerous and widespread regions of hypoactivation in the present analysis was most likely due to the inclusion of double the number of articles and more than double the number of participants, greatly enhancing statistical power over the earlier meta-analysis.

The final cluster of face-related hypoactivation in ASD was found within the left calcarine fissure (745 voxels) – an area associated with early visual processing of the right visual field (Wandell et al., 2007). Research has long established a left visual field bias in neurotypical face perception, which has been taken to reflect right hemisphere lateralization of this cognitive domain (Gilbert & Bakan, 1973; Yovel et al., 2008). Interestingly, previous work has shown a lack of this left visual field bias in ASD (Dundas et al., 2012). In light of this previous research, face-related hypoactivation within the left calcarine fissure was unexpected. However, this cluster partially overlapped with the lingual gyrus, where Herringshaw et al. (2016) reported language hyperactivation that was not observed in the present analysis. Future work should elucidate the relevance of this finding.

In further support of the hypothesis of reduced lateralization in ASD, the largest cluster of face-related hyperactivation in ASD was found within the left middle occipital gyrus (748 voxels), adjacent to the putative location of the aforementioned OFA. Face-related hyperactivation was also found in the bilateral anterior cingulate (122 voxels), left striatum and caudate nucleus (105 voxels), and left middle temporal gyrus (82 voxels). The anterior cingulate and striatum have been associated with the salience network (Seeley, 2019), while the middle

temporal gyrus has been associated with face processing (Haxby et al., 2000). The only right hemisphere cluster of face-related hyperactivation in ASD was located within the right middle frontal gyrus (42 voxels).

The most striking evidence that ASD is related to atypical hemispheric asymmetry of both language and face processing came from the assessment of between-group overlap across cognitive domains. Overlaying the brain maps of between-group differences (i.e., ASD>TD and TD>ASD) separately for each cognitive domain (i.e., language and face processing) revealed clusters around the STS in both the left (58 voxels) and right (110 voxels) hemispheres that showed a crossover double dissociation between language and face processing in ASD relative to TD groups: 1) The left hemisphere region showed language-related hypoactivation and face-related hyperactivation in ASD; 2) The right hemisphere region showed face-related hypoactivation and language-related hyperactivation in ASD.

The pSTS was further implicated by the domain conjunction analysis of within-group contrasts, which examined whether any brain regions were reliably engaged in both language and face processing in either group. There were no areas associated with both language and face processing in TD groups. However, one cluster within the right pSTS (119 voxels) was concordantly associated with both cognitive domains in ASD groups across studies.

Research has shown that the pSTS is critical for processing the dynamic aspects of faces, multisensory integration, biological motion, and theory of mind,

which are all cognitive functions that are frequently impacted in ASD (Frith, 2001; Koldewyn et al., 2011; Yang et al., 2015). Studies have also shown that pSTS activity predicts ASD traits in TD individuals (Hasegawa et al., 2013; Nummenmaa et al., 2012). Interestingly, recent work has suggested the existence of a third visual pathway specialized for social perception, beyond the ventral and dorsal streams, that projects from early visual cortex to the pSTS via motion selective areas (Pitcher & Ungerleider, 2021). Results of the present meta-analysis suggest that reduced hemispheric specialization of the pSTS is an important aspect of atypical functional brain organization in ASD.

The assessment of between-group overlap across domains also revealed a cluster in the right ACC (29 voxels) that was associated with both language-related hypoactivation and face-related hyperactivation in ASD. The ACC has been implicated in a wide range of cognitive functions, including attention, emotion, decision-making, impulse control, and error monitoring (Allman et al., 2001; Bush et al., 2000). Functionally and structurally distinct subregions of the ACC have been delineated (e.g., rostral/causal, ventral/dorsal/, and supracallosal/subcallosal distinctions) that show different patterns of functional connectivity with large-scale brain networks, including the default network and frontoparietal control network (Margulies et al., 2007). The ACC has particularly been associated with the salience network, which has consistently been reported to be altered in ASD (Green et al., 2016).

The present meta-analysis demonstrated that ASD is associated with reduced hemispheric specialization of both language and face processing, which was particularly evident in the STS in both hemispheres. Due to the nature of quantitative meta-analyses, these cognitive domains were examined in general, across different levels and types of processing in variable experimental contexts. However, the results should inform future empirical work aiming to investigate particular components of language (e.g., reading, listening, or generating) and face processing (e.g., identity or emotion discrimination of static or dynamic stimuli). Importantly, these findings suggest that atypical development of hemispheric specialization may be a fundamental factor underlying the clinical hallmarks of ASD.

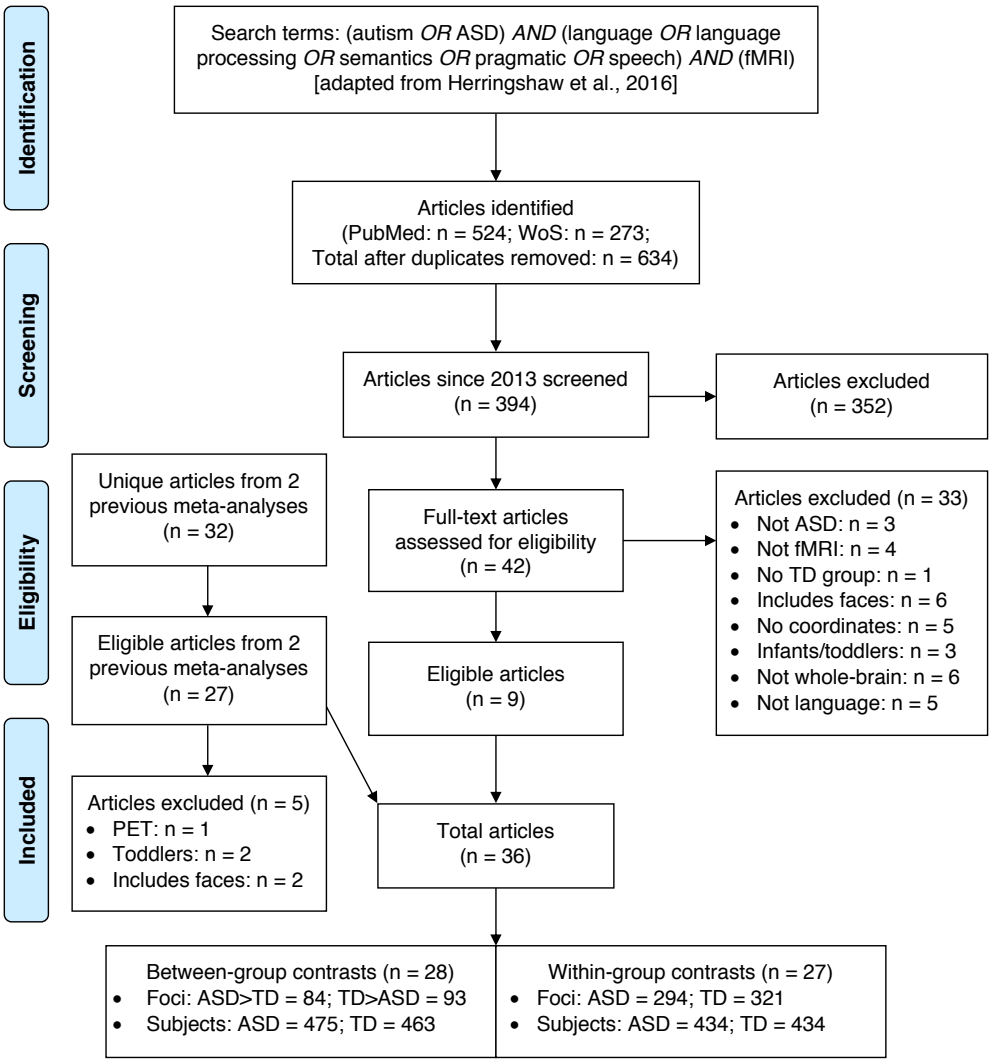

Figure 2.1. PRISMA flowchart for determining language article eligibility (adapted from Moher et al., 2009). This search included articles published up to and including Dec. 31, 2020. The search performed by Herringshaw et al. (2016) included articles published between 1999-2014. Thus, the present search screened articles published since 2013 to ensure no potentially eligible papers were missed. ASD = autism spectrum disorder; TD = typically developing; n = number of articles; WoS = Web of Science; fMRI = functional magnetic resonance imaging; PET = positron emission tomography.

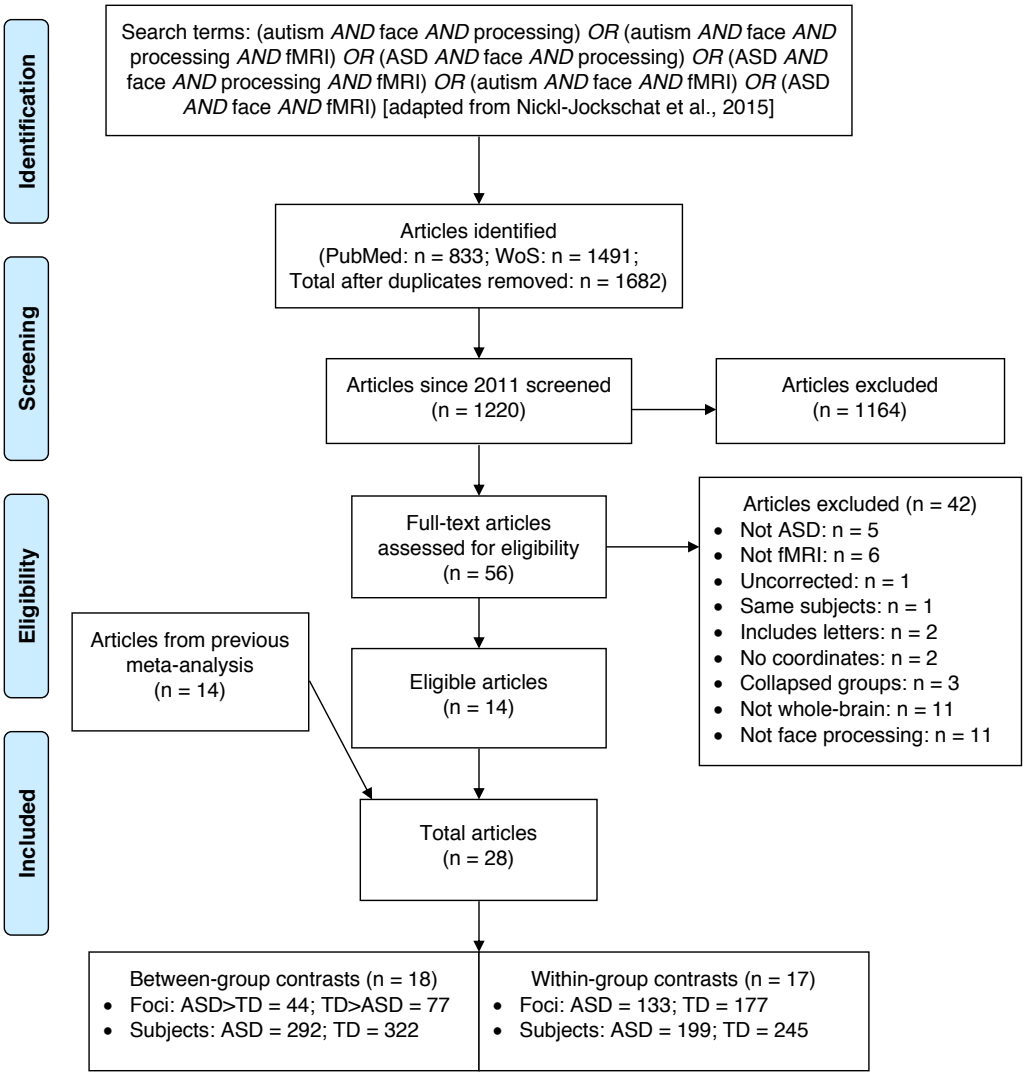

Figure 2.2. PRISMA flowchart for determining face processing article eligibility (adapted from Moher et al., 2009). This search included articles published up to and including Dec. 31, 2020. The prior search by Nickl-Jockschat et al. (2015) included articles published between 2001-2012. Thus, the present search screened articles published since 2011 to ensure that no potentially eligible papers were missed. ASD = autism spectrum disorder; TD = typically developing; n = number of articles; WoS = Web of Science; fMRI = functional magnetic resonance imaging.

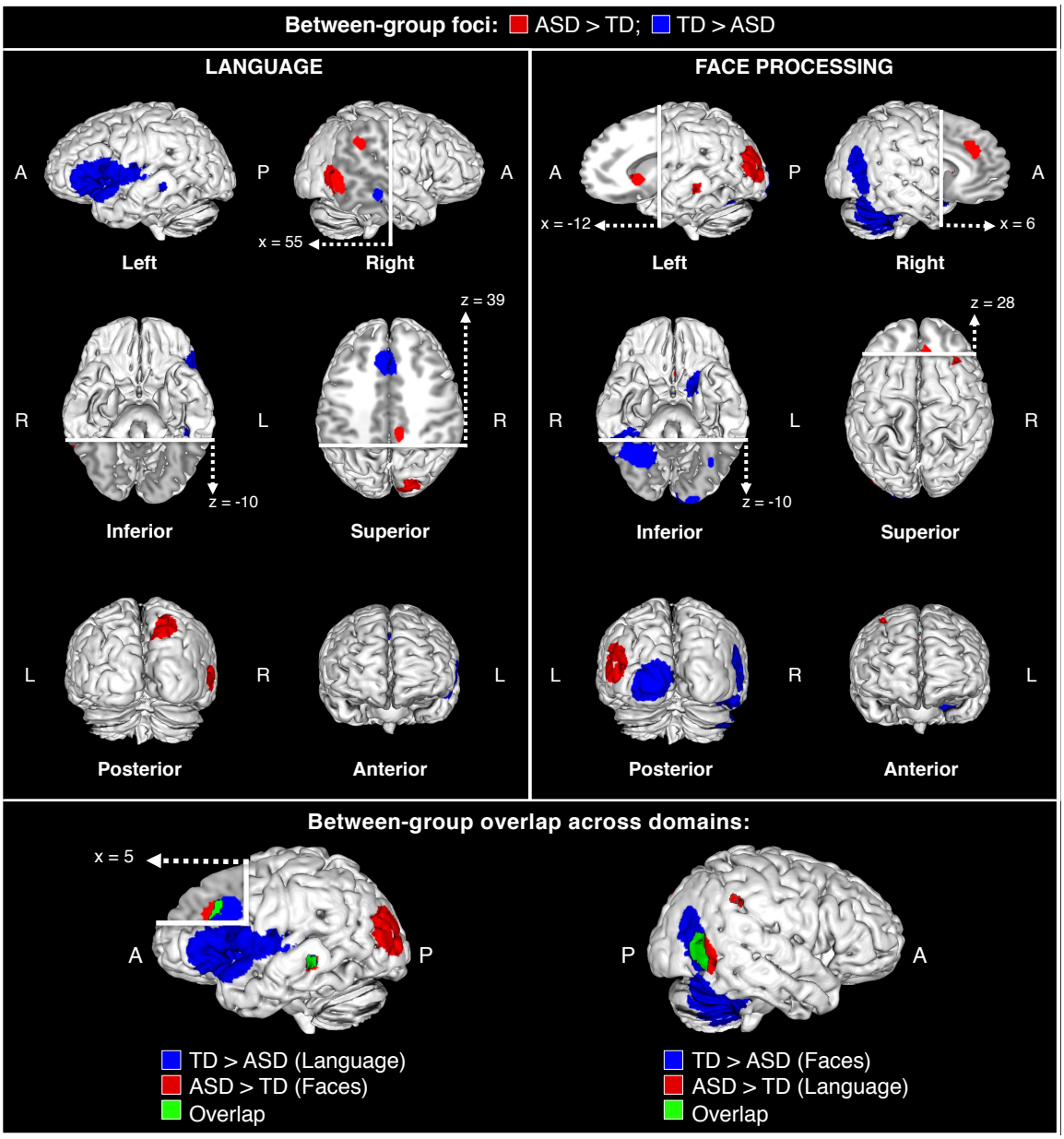

Figure 2.3. Top: Foci from between-group contrasts. Bottom: Cluster overlap across domain (language & face processing) and group (ASD>TD & TD>ASD). White bars and arrows with hashed lines indicate slice planes where the inflated brain surfaces have been cut to display medial clusters. ASD = autism spectrum disorder; TD = typically developing; A = anterior; P = posterior; L = left; R = right.

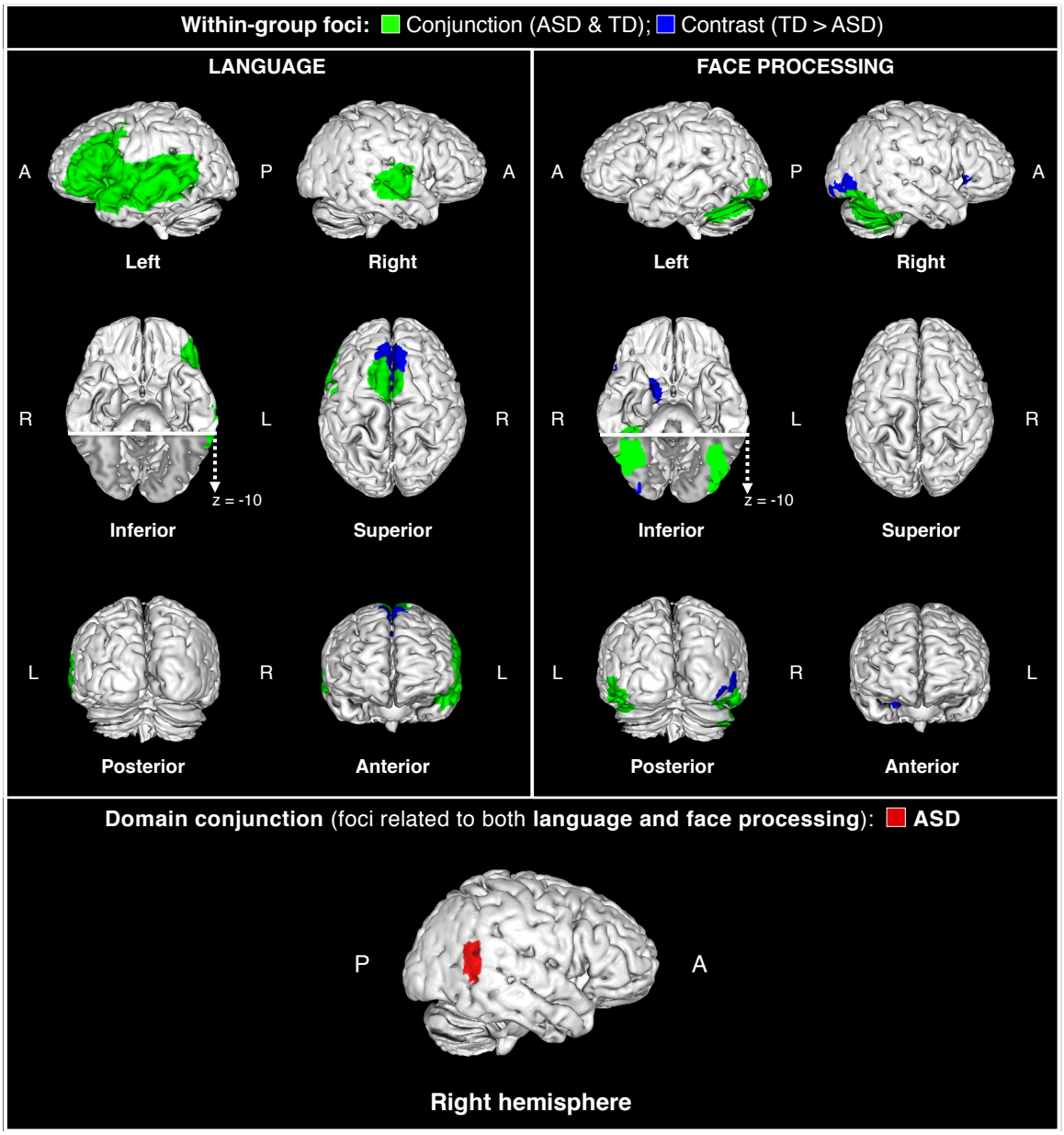

Figure 2.4. Top: Conjunction and contrast analyses of foci from within-group contrasts. Bottom: Domain conjunction, i.e., clusters related to both language and face processing. Note: Contrast analyses of within-group foci revealed no clusters where ASD>TD for either language or face processing, and the domain conjunction revealed no clusters related to both cognitive domains in TD groups. White bars and arrows with hashed lines indicate slice planes where the inflated

brain surfaces have been cut to display medial clusters. ASD = autism spectrum disorder; TD = typically developing; A = anterior; P = posterior; L = left; R = right.

Table 2.1

Summary of participants in 36 included articles on language

Study	Group *n* (*n* female)	Age Mean (SD)	Age Range	IQ Mean (SD)	Handedness	Diagnostic Measure
Anderson et al. (2010)	ASD: 15 (0) TD: 26 (0)	ASD: 21.7 (6.4) TD: 22.5 (6.3)	ASD: 12–35 TD: 9–32	ASD: 106 (22.2) TD: 121.8 (12.7)	RH	ADOS, ADI-R
Bednarz et al. (2017)	ASD: 18 (4) TD: 13 (4)	ASD: 10.7 (1.6) TD: 10.5 (1.8)	ASD: 8.1–13.8 TD: 8.1–14.1	ASD: 94.4 (15.5) TD: 97.9 (9.9)	RH	ADOS, ADI-R, Clinician
Catarino et al. (2010)	ASD: 12 (0) TD: 12 (0)	ASD: 27 (10) TD: 34 (13)	ASD: 16–44 TD: 18–57	ASD: 113 (15) TD: 120 (12)	RH	ADI-R, Clinician
Chen et al. (2016)	ASD: 37 (0) TD: 35 (0)	ASD: 13.3 (2.4) TD: 13.3 (2.7)	8–18	ASD: 102.6 (12.8) TD: 106.9 (11.2)	RH	DSM-IV
Chouinard et al. (2017)	ASD: 12 (3) TD: 12 (4)	ASD: 32.4 (10.8) TD: 33.0 (10.1)	ASD: 16–49 TD: 19–50	ASD: 116.7 (7.8) TD: 111.7 (10.8)	ASD: 7R/1L/4A TD: 9R/1L/2A	ADOS-2, AQ
Colich et al. (2012)	ASD: 16 (2) TD: 16 (2)	ASD: 14.27 (2.5) TD: 13.15 (2.2)	NR	ASD: 108 (13) TD: 109 (13)	RH	ADOS, ADI-R
Eigsti et al. (2012)	ASD: 16 (2) TD: 11 (4)	ASD: 13.7 (2.8) TD: 13.7 (2.6)	9–17	ASD: 96.7 (14.9) TD: 111.9 (10.9)	18R, 2L, 7 NR	ADOS, ADI-R, Clinician
Eigsti et al. (2016)	ASD: 23 (1) TD: 20 (3)	ASD: 13.9 (3.3) TD: 13.3 (2.8)	ASD: 8–20 TD: 9–21	ASD: 105 (15) TD: 112 (12)	35R, 5L, 3 NR	ADOS, ADI-R, Clinician
Gaffrey et al. (2007)	ASD: 10 (0) TD: 10 (0)	ASD: 26.1 (10.5) TD: 25.3 (9.8)	ASD: 14–44 TD: NR	ASD: 101.5 (11.9) TD: 112.6 (12.6)	16R, 4L	ADOS, ADI-R, DSM-IV
Gebauer et al. (2014)	ASD: 19 (2) TD: 20 (2)	ASD: 26.16 (5.6) TD: 24.45 (4.6)	ASD: 20–36 TD: 19–41	ASD: 108.32 (14.56) TD: 114.50 (12.4)	RH	ADOS, Clinician
Groen et al. (2010)	ASD: 16 (4) TD: 26 (5)	ASD: 15.3 (1.6) TD: 15.7 (1.7)	12–18	ASD: 100.4 (20.6) TD: 105.3 (8.7)	RH	ADI-R
Harris et al. (2006)	ASD: 14 (0) TD: 22 (0)	ASD: 36 (12) TD: 31 (9)	ASD:18–52 TD: 19–50	ASD: 116 (8) TD: 122 (9)	RH	ADOS, ADI-R, Clinician
Hernandez et al. (2020)	ASD: 26 (7) TD: 28 (11)	ASD: 13.75 (2.98) TD: 13.78 (2.66)	8–18	ASD: 102.32 (14.92) TD: 113.11 (13.05)	NR	ADOS, ADI-R
Hesling et al. (2010)	ASD: 8 (0) TD: 8 (0)	ASD: 23.38 (2.10) TD: 23.05 (2.02)	NR	ASD: 89 (7.89) TD: 128.33 (4.58)	NR	ADI-R, DSM-IV
Hubbard et al. (2012)	ASD: 10 (0) TD: 10 (0)	ASD: 13 (2.1) TD: 12 (1.6)	NR	ASD: 110 (14) TD: 116 (10)	RH	ADI-R, ADOS-G
Jochaut et al. (2015)	ASD: 13 (NR) TD: 13 (NR)	ASD: 20.67 (6.77) TD: 22.92 (8.14)	ASD: 17–40 TD: 16–38	ASD: 83.61 (25.27) TD: 104 (11.28)	NR	DSM-IV, ADI-R

Table 2.1 (continued)

Summary of participants in 36 included articles on language

Study	Group *n* (*n* female)	Age Mean (SD)	Age Range	IQ Mean (SD)	Handedness	Diagnostic Measure
Just et al. (2004)	ASD: 17 (NR) TD: 17 (NR)	ASD: NR TD: NR	NR	ASD: NR; TD: NR Both groups: 80+	30R, 4L	ADI, ADOS, Clinician
Kana & Wadsworth (2012)	ASD: 16 (0) TD: 16 (0)	ASD: 20 (6.43) TD: 21.6 (2.70)	16–35	ASD: 130.80 (16.84) TD: 113.44 (9.18)	RH	ADOS, ADI-R,
Kana et al. (2006)	ASD: 12 (1) TD: 13 (1)	ASD: 22.5 (8.8) TD: 20.3 (4.0)	NR	ASD: 110.7 (9.2) TD: 113.2 (9.2)	ASD: 10R/2L TD: 11R/2L	ADOS-G, ADI-R
Kana et al. (2017)	ASD: 15 (0) TD: 15 (0)	ASD: 21.63 (5.54) TD: 27.25 (5.19)	ASD: 15–36 TD: 16–34	ASD: 104 (13.76) TD: 114.29 (7.01)	RH	ADOS, ADI-R, SRS
Kenworthy et al. (2013)	ASD: 17 (0) TD: 20 (0)	ASD: 16.03 (2.56) TD: 17.05 (2.10)	ASD: 12–21 TD: 12–23	ASD: 111.81 (15.86) TD: 113.25 (9.20)	ASD: 15R/2L TD: 17R/3L	ADOS, ADI-R
Kim et al. (2018)	ASD: 15 (1) TD: 18 (8)	ASD: 9.66 (2.19) TD: 10.47 (2.78)	NR	ASD: 103.87 (11.67) TD: 109.33 (15.81)	RH	ADOS, ADI-R
Kleinhans et al. (2008)	ASD: 14 (0) TD: 14 (0)	ASD: 23.79 (9.58) TD: 22.41 (8.67)	ASD: 14–44 TD: 14–43	ASD: 98.14 (11.84) TD: 113.43 (12.91)	ASD: 11R/2L/1A TD: 13R/1L	ADOS-G, ADI-R
Knaus et al. (2008)	ASD: 12 (0) TD: 12 (0)	ASD: 15.46 (2.48) TD: 14.94 (2.71)	ASD: 11.4–19.8 TD: 11.5–19.8	ASD: 105.42 (19.35) TD: 122.25 (11.10)	RH	ADOS, ADI-R
Knaus et al. (2017)	ASD: 15 (3) TD: 19 (3)	ASD: 13.57 (1.97) TD: 12.64 (1.37)	11–16	ASD: 91.87 (11.38) TD: 106.11 (10.74)	28R, 6L/A	ADOS-2, ADI-R, SCQ
Lai et al. (2012)	ASD: 12 (2) TD: 12 (3)	ASD: 12.40 (4.69) TD: 12.06 (4.03)	ASD: 7.01–22.47 TD: 4.19–17.78	ASD: NR TD: NR	ASD: 10R/1L/1A TD: 11R/1L	DSM IV, ADI-R
Mason et al. (2008)	ASD: 18 (1) TD: 18 (2)	ASD: 26.5 (NR) TD: 27.4 (NR)	NR	ASD: 101.9 (NR) TD: 105.5 (NR)	31R, 3L	ADOS-G, ADI-R
Mizuno et al. (2011)	ASD: 15 (1) TD: 15 (0)	ASD: 24.7 (7.8) TD: 24.7 (7.7)	NR	ASD: 106.3 (10.7) TD: 108.7 (5.1)	ASD: 11R/4L TD: 14R/1L	ADOS, ADI-R
Moseley et al. (2015)	ASD: 18 (0) TD: 18 (0)	ASD: 30.4 (10) TD: 28.6 (11.7)	NR	ASD: 113.5 (23) TD: 110.2 (12.3)	RH	Clinician, DSM-IV, AQ
Murdaugh et al. (2016)	ASD: 26 (5) TD: 19 (5)	ASD: 10.9 (1.34) TD: 10.6 (1.59)	NR	ASD-1: 94.1 (11.23) ASD-2: 97.9 (15.91) TD: 96.2 (10.89)	RH	ADOS, ADI-R
Schelinski et al. (2016)	ASD: 16 (3) TD: 16 (3)	ASD: 33.75 (10.12) TD: 33.69 (9.58)	ASD: 20–51 TD: 18–52	ASD: 110.31 (13.79) TD: 111.5 (10.97)	28R, 4L	ADOS-G, ADI-R, SCQ, ICD-10 (Ger)

Table 2.1 (continued)

Summary of participants in 36 included articles on language

Study	Group *n* (*n* female)	Age Mean (SD)	Age Range	IQ Mean (SD)	Handedness	Diagnostic Measure
Sharda et al. (2014)	ASD: 22 (6) TD: 22 (6)	ASD: 11.0 (3.4) TD: 10.4 (2.4)	ASD: 6–16 TD: 7–16	ASD: 83.14 (17.8) TD: 100.27 (11.6)	43R, 1L	ADOS, CARS II, DSM-IV
Scott-VanZeeland et al. (2010)	ASD: 18 (0) TD: 18 (0)	ASD: 12.62 (2.50) TD: 11.64 (1.58)	NR	ASD: 102.17 (19.82) TD: 104.00 (12.36)	NR	ADOS-G, ADI-R
Shen et al. (2012)	ASD: 14 (0) TD: 14 (0)	ASD: 24.1 (9.5) TD: 24.2 (8.4)	ASD: 15–44 TD: 14–42	ASD: 93 (15.5) TD: 110 (10.8)	22R, 6L	ADOS, ADI-R, DSM-IV
Tesink et al. (2011)	ASD: 24 (8) TD: 24 (8)	ASD: 26.3 (6.3) TD: 26.2 (6.0)	ASD: 18–40	ASD: 114.3 (14.1) TD: 119.9 (11.7)	RH	ADI-R, DSM-IV
Wang et al. (2006)	ASD: 18 (0) TD: 18 (0)	ASD: 11.9 (2.8) TD: 11.9 (2.3)	ASD: 7.4–16.9 TD: 8.1–15.7	ASD: 102 (18) TD: 106 (14)	RH	ADOS-G, ADI-R

Note. ASD = autism spectrum disorder; TD = typically developing; n = number of participants; SD = standard deviation; NR = not reported; RH = right handed; R = right; L = left; A = ambidextrous; IQ = intelligence quotient; ADOS(-G) = Autism Diagnostic Observation Schedule(-Generic); ADI(-R) = Autism Diagnostic Interview(-Revised); AQ = Autism Spectrum Quotient; DSM-IV = Diagnostic and Statistical Manual-IV; ICD-10 = International Statistical Classification of Diseases; SRS = Social Responsiveness Scale; SCQ = Social Communication Questionnaire; CARS = Childhood Autism Rating Scale; Ger = German.

Table 2.2

Summary of participants in 28 included articles on face processing

Study	Group *n* (*n* female)	Age Mean (SD)	Age Range	IQ Mean (SD)	Handedness	Diagnostic Measure
Ashwin et al. (2007)	ASD: 13 (0) TD: 13 (0)	ASD: 31.2 (9.1) TD: 25.6 (5.1)	NR	ASD: 108.6 (17.1) TD: 117.9 (9.6)	RH	Clinician diagnosed
Bird et al. (2006)	ASD: 16 (2) TD: 16 (2)	ASD: 33.3 (11.5) TD: 35.3 (12.1)	NR	ASD: 119 (14) TD: 119 (13.2)	NR	ADOS, DSM-IV, AQ
Bookheimer et al. (2011)	ASD: 12 (0) TD: 12 (0)	ASD: 11.3 (4.0) TD: 11.9 (2.4)	ASD: 7.8–19.6 TD: 8.1–15.7	ASD: (WV) 9.8 (2.5) TD: (WV) 13.6 (2.7)	NR	ADOS, ADI-R, PPVT-III
Brandenburg-Goddard et al. (2014)	ASD: 17 (0) TD: 19 (0)	ASD: 12.41 (1.94) TD: 12.03 (2.36)	10–18	ASD: 96.5 (3.7) TD: 103.9 (3.5)	NR	ADI-R, SRS
Chanel et al. (2016)	ASD: 15 (2) TD: 14 (2)	ASD: 28.6 (1.87) TD: 31.6 (2.61)	ASD: 19–43 TD: 19–53	ASD: 108.06 (4.5) TD: 116.78 (4.6)	ASD: 12R/3L TD: 10R/4L	ADOS
Corradi-Dell'Acqua et al. (2014)	ASD: 10 (0) TD: 10 (0)	ASD: 21.5 (NR) TD: 21.55 (NR)	ASD: 19.5–23.5 TD: 19.98–24.84	ASD: 100.9 (NR) TD: 109.5 (NR)	NR	ADOS-G, ADI-R
Critchley et al. (2000)	ASD: 9 (0) TD: 9 (0)	ASD: 37 (7) TD: 27 (7)	NR	ASD: 102 (15) TD: 116 (10)	RH	ADI, ICD-10
Dalton et al. (2005): Exp 1	ASD: 14 (0) TD: 12 (0)	ASD: 15.9 (4.71) TD: 17.1 (2.78)	NR	ASD: 94 (19.47) TD: 100 (15)	NR	ADI-R, DSM-IV
Dalton et al. (2005): Exp 2	ASD: 16 (0) TD: 16 (0)	ASD: 14.5 (4.60) TD: 14.5 (4.56)	NR	ASD: 92.1 (27.7) TD: 123.1 (12.74)	NR	ADI-R, DSM-IV
Dapretto et al. (2006)	ASD: 10 (1) TD: 10 (1)	ASD: 12.05 (2.5) TD: 12.38 (2.2)	NR	ASD: 96.4 (18.3) TD: 106.7 (15.9)	NR	ADOS-G, ADI-R
Deeley et al. (2007)	ASD: 9 (0) TD: 9 (0)	ASD: 34 (10) TD: 27 (5)	NR	ASD: 114 (12) TD: 120 (18)	17R, 1A	ADOS, ADI, ICD-10
Dichter & Belger (2007)	ASD: 15 (1) TD: 16 (1)	ASD: 22.9 (5.2) TD: 23.2 (5.7)	NR	ASD: 105.0 (18.6) TD: 105.7 (15.0)	RH	ADOS, ADI-R
Herrington et al. (2015)	ASD: 12 (NR) TD: 19 (NR)	ASD: 13.4 (4.2) TD: 13.4 (3.5)	NR	ASD: 108.8 (14.8) TD: 114.8 (10.8)	NR	ADOS-G, ADI-R
Hubl et al. (2003)	ASD: 10 (0) TD: 10 (0)	ASD: 27.7 (7.8) TD: 25.3 (6.9)	NR	ASD: 98 (17) TD: 112 (9)	NR	ADOS (German), ADI-R
Joseph et al. (2015)	ASD: 12 (1) TD: 12 (1)	ASD: 13.5 (3.3) TD: 13.0 (3.45)	NR	ASD: 96.1 (26.5) TD: 115.1 (15.8)	22R, 1L, 1A	ADOS, ADI-R, SRS, PPVT
Klapwijk et al. (2015)	ASD: 23 (0) TD: 33 (0)	ASD: 17.0 (1.2) TD: 17.1 (1.2)	15–19	ASD: 107.1 (10.4) TD: 97.2 (9.2)	RH	ADOS-G, ADI-R

Table 2.2 (continued)

Summary of participants in 28 included articles on face processing

Study	Group *n* (*n* female)	Age Mean (SD)	Age Range	IQ Mean (SD)	Handedness	Diagnostic Measure
Koshino et al. (2008)	ASD: 11(0) TD: 11 (1)	ASD: 24.5 (10.2) TD: 28.7 (10.9)	NR	ASD: 104.5 (13.1) TD: 108.6 (9.1)	ASD: 9R/2L TD: 10R/1L	ADOS, ADI-R
Kryza-Lacombe et al. (2019)	ASD: 47 (6) TD: 73 (20)	ASD: 13.94 (2.35) TD: 14.40 (2.90)	8.3–19.2	ASD: 106 (20.36) TD: 101.39 (12.69)	NR	ADOS, ADI-R
Odriozola et al. (2016)	ASD: 20 (2) TD: 20 (4)	ASD: 10.51 (1.52) TD: 9.72 (1.61)	NR	ASD: 110.20 (16.12) TD: 119.53 (15.1)	ASD: RH TD: 19R/1A	ADOS, ADI-R
Okamoto et al. (2017)	ASD: 17 (1) TD: 17 (1)	ASD: 24.2(4.3) TD: 24.2 (3.9)	NR	ASD: 107.3 (13.3) TD: 111.5 (6.1)	RH	Clinician, DISCO
Pelphrey et al. (2007)	ASD: 8 (2) TD: 8 (2)	ASD: 24.5 (11.5) TD: 24.1 (5.6)	ASD: 17.9–50.3 TD: 18.1–32.2	ASD: 113 (11) TD: 120 (9)	RH	ADOS, ADI-R
Perlman et al. (2011)	ASD: 12 (1) TD: 7 (0)	ASD: 25.5 (7.47) TD: 28.57 (5.74)	ASD: 18–37 TD: 22–37	ASD: 102.2 (15.8) TD: 112.0 (6.7)	ASD: 11R/1L TD: 7R	ADOS, ADI-R
Pierce et al. (2004)	ASD: 7 (0) TD: 10 (0)	ASD: 27.1 (9.2) TD: NR	ASD: 16–42 TD: 16–40	ASD: 80.3 (17.7) TD: NR	ASD: 5R/1L/1A TD: NR	ADOS, ADI, ADI-R, DSM-IV
Scherf et al. (2015)	ASD: 20 (0) TD: 12 (0)	ASD: 14.1 (NR) TD: 13.8 (NR)	10–17	ASD: 108.5 (NR) TD: 117.6 (NR)	ASD: 16R/4L TD: 10R/2L	ADOS, ADI-R
Schulte-Ruther et al. (2011)	ASD: 18 (0) TD: 18 (0)	ASD: 27.4 (9.3) TD: 25.1 (6.7)	ASD: 18–48 TD: 19–46	ASD: 106.6 (10.5) TD: 112.1 (10.4)	NR	ADOS, DSM-IV, AQ, EQ
Wang et al. (2004)	ASD: 12 (0) TD: 12 (0)	ASD: 12.2 (4.8) TD: 11.8 (2.5)	ASD: 8–23 TD: 8–16	ASD: 12.1 (4.6) TD: 16.3 (5.9)	RH	ADOS-G, ADI-R
Weng et al. (2011)	ASD: 22 (5) TD: 20 (1)	ASD: 14.36 (1.70) TD: 14.97 (1.95)	ASD: 11.17–16.75 TD: 10.25–18	ASD: 114 (13.76) TD: 105 (11.35)	ASD: 19R/3L TD: 18R/2L	ADOS, ADI-R
Whyte et al. (2016)	ASD: 14 (1) TD: 14 (1)	ASD: 15 (2) TD: 15 (2)	13–18	ASD: 112 (11) TD: 110 (12)	ASD: 12R/2L TD: 12R/2L	ADOS, ADI-R
Zurcher et al. (2013)	ASD: 16 (3) TD: 18 (2)	ASD: 23.5 (6.8) TD: 25.8 (5.3)	NR	ASD: 108.7 (13.3) TD: 112.1 (9.0)	NR	ADOS, ADI-R, RPM

Note. ASD = autism spectrum disorder; TD = typically developing; n = number of participants; SD = standard deviation; NR = not reported; RH = right handed; R = right; L = left; A = ambidextrous; IQ = intelligence quotient; WV = Wechsler Vocabulary; Exp = experiment; ADOS(-G) = Autism Diagnostic Observation Schedule(-Generic); ADI(-R) = Autism Diagnostic Interview(-Revised); AQ = Autism Spectrum Quotient; DSM-IV = Diagnostic and Statistical Manual-IV; ICD-10 = International Statistical Classification of Diseases; SRS = Social Responsiveness Scale; PPVT = Peabody Picture Vocabulary Test; DISCO = Diagnostic Interview for Social and Communication Disorders; EQ = Empathy Questionnaire; RPM = Raven's Progressive Matrices.

Table 2.3

Summary of contrasts and foci in 36 included articles on language

Study	Contrast	Task	Stimulus Details	Foci			
				ASD	TD	ASD>TD	TD>ASD
Anderson et al. (2010)	listening to sentences > rest	listen to phrases, think of word described	listen + generate	18	18	1	1
Bednarz et al. (2017)	word (similar + dissimilar) > fixation	is word same category as others presented	read	5	7	n/a	n/a
Catarino et al. (2010)	incongruent > congruent concrete sentences	is final word congruent with rest of sentence	read + generate	3	4	n/a	n/a
Chen et al. (2016)	word relatedness > perceptual control	indicate if two words are related in meaning	read	2	5	1	1
Chouinard et al. (2017)	metaphors > scrambled metaphors	indicate if statements are literally true	listen + generate	19	14	6	n/a
Colich et al. (2012)	sincere + insincere statements > baseline	indicate if statements are ironic or sincere	listen	29	32	n/a	15
Eigsti et al. (2012)	angry statements + questions > neutral	indicate if sentence is about a living creature	listen	2	2	5	1
Eigsti et al. (2016)	low imagery statements > baseline	indicate if sentences are true or false	read	n/a	n/a	7	n/a
Gaffrey et al. (2007)	semantic > perceptual decision	indicate if word is from a certain category	read	13	32	11	n/a
Gebauer et al. (2014)	happy > neutral prosody	rate prosody on a scale of happy to sad	listen	n/a	n/a	4	1
Groen et al. (2010)	normal sentence > speech-like noise	button press for pseudoword sentence	listen	4	7	1	n/a
Harris et al. (2006)	semantic > perceptual word task	indicate if words are positive or negative	read	3	7	n/a	n/a
Hernandez et al. (2020)	conversation in noise > conversation + noise	passively listen to conversations + noise	listen	18	2	3	n/a
Hesling et al. (2010)	prosodic speech > rest	passively listen to story with and without noise	listen	4	6	1	3
Hubbard et al. (2012)	still frame with speech > still frame without speech	hear recordings of natural speech + hand gestures	listen/watch video	5	8	n/a	n/a
Jochaut et al. (2015)	speech envelope > rest	watch TV program on dangers of sun exposure	listen/watch video	n/a	n/a	n/a	1

Table 2.3 (continued)

Summary of contrasts and foci in 36 included articles on language

Study	Contrast	Task	Stimulus Details	Foci			
				ASD	TD	ASD>TD	TD>ASD
Just et al. (2004)	sentence comprehension > baseline	identify agent or recipient of sentence action	read	10	8	n/a	n/a
Kana & Wadsworth (2012)	low imagery statements > baseline	indicate if sentences are true or false	read	n/a	n/a	4	n/a
Kana et al. (2006)	self task > letter task	answer questions about presented adjectives	read + generate	n/a	n/a	11	1
Kana et al. (2017)	puns > baseline	passively read puns and literal sentences	read	2	5	n/a	3
Kenworthy et al. (2013)	word generation > baseline	indicate if sentences are true or false	read + generate	n/a	n/a	n/a	19
Kim et al. (2018)	sentence + picture pairs > baseline	determine if sentence and picture match	read	n/a	n/a	1	3
Kleinhans et al. (2008)	word generation > baseline	think of words starting with a letter or category	generate	4	4	3	1
Knaus et al. (2008)	synonym > symbol judgment	indicate which of 2 verbs is most like a target word	read	8	7	11	n/a
Knaus et al. (2017)	response naming > visual processing	read phrases and think of word being described	read + generate	2	4	n/a	n/a
Lai et al. (2012)	listening to speech > baseline	listen to recording of parent speaking	listen	4	20	n/a	14
Mason et al. (2008)	intentional inference > baseline	read sentences and answer yes/no questions	read	63	44	n/a	n/a
Mizuno et al. (2011)	deictic shifting > baseline	respond in 1st or 2nd person perspective	read + generate	14	9	6	n/a
Moseley et al. (2015)	emotion words > baseline	silently read briefly presented words	read	n/a	n/a	n/a	13
Murdaugh et al. (2016)	low imagery > baseline	indicate if sentences are true or false	read	7	10	n/a	4
Schelinski et al. (2016)	voice identity task > baseline	indicate if sentences are spoken by target speaker	listen	23	24	n/a	6

Table 2.3 (continued)

Summary of contrasts and foci in 36 included articles on language

Study	Contrast	Task	Stimulus Details	Foci			
				ASD	TD	ASD>TD	TD>ASD
Sharda et al. (2014)	word segmentation > baseline	listen to artificial speech containing syllable sets	listen	n/a	n/a	n/a	1
Scott-VanZeeland et al. (2010)	listening to spoken words > rest	passively listen to presented words	listen	n/a	4	n/a	5
Shen et al. (2012)	lexicosemantic decision > letter task	indicate if words belong to target categories	read	3	14	2	n/a
Tesink et al. (2011)	correct sentences > reversed speech	listen to sentences and answer questions later	listen	10	8	n/a	n/a
Wang et al. (2006)	event knowledge, prosodic cues, both > baseline	indicate if statements are ironic or sincere	listen	19	16	6	n/a

Note. ASD = autism spectrum disorder; TD = typically developing; n/a = not available.

Table 2.4

Summary of contrasts and foci in 28 included articles on face processing

Study	Contrast	Task	Stimulus Details	Foci			
				ASD	TD	ASD>TD	TD>ASD
Ashwin et al. (2007)	neutral + fearful faces > scrambled	button press with each presented image	static greyscale	1	5	6	3
Bird et al. (2006)	faces > houses	selective attention and identity discrimination	static greyscale	5	5	n/a	n/a
Bookheimer et al. (2011)	upright faces > forms	identity matching	static greyscale	6	10	n/a	n/a
Brandenburg-Goddard et al. (2014)	face matching > object matching	expression matching	static colour	n/a	3	n/a	n/a
Chanel et al. (2016)	emotion x gaze > baseline	button press for inverted faces (oddball paradigm)	static colour	n/a	n/a	3	5
Corradi-Dell'Acqua et al. (2014)	faces > houses	gender discrimination	static greyscale	4	5	n/a	n/a
Critchley et al. (2000)	emotion x gender > baseline	expression and gender discrimination	static greyscale	n/a	n/a	2	1
Dalton et al. (2005): Exp 1	faces > baseline	expression discrimination	static greyscale	n/a	n/a	2	5
Dalton et al. (2005): Exp 2	faces > baseline	familiarity judgement	static greyscale	n/a	n/a	1	4
Dapretto et al. (2006)	faces > baseline	expression discrimination	static colour	10	14	n/a	n/a
Deeley et al. (2007)	faces > baseline	expression discrimination	static greyscale	n/a	n/a	n/a	8
Dichter & Belger (2007)	incongruent > congruent gaze	gaze discrimination	static greyscale	2	8	n/a	n/a
Herrington et al. (2015)	faces > houses	selective attention and one-back identity discrimination	static greyscale	n/a	n/a	15	n/a
Hubl et al. (2003)	faces > scrambled	expression and gender discrimination	static greyscale on colour background	11	12	n/a	n/a
Joseph et al. (2015)	faces > textures (age covariate)	button press with each presented image	static greyscale	2	2	n/a	n/a
Klapwijk et al. (2015)	face emotion > width	expression discrimination	static colour	n/a	n/a	n/a	3

Table 2.4 (continued)

Summary of contrasts and foci in 28 included articles on face processing

Study	Contrast	Task	Stimulus Details	Foci			
				ASD	TD	ASD>TD	TD>ASD
Koshino et al. (2008)	faces > baseline	n-back (0-back, 1-back, 2-back)	static greyscale	9	15	3	20
Kryza-Lacombe et al. (2019)	irritability x emotion > baseline	gender discrimination	static colour	n/a	n/a	1	n/a
Odriozola et al. (2016)	deviant faces > deviant scenes	identity discrimination (oddball paradigm)	static colour	n/a	n/a	1	n/a
Okamoto et al. (2017)	faces > bodies, scenes, cars	colour detection of fixation cross	static greyscale	2	3	n/a	n/a
Pelphrey et al. (2007)	dynamic > static facial expressions	button press with each presented face	static greyscale	1	5	n/a	6
Perlman et al. (2011)	free view 1 fearful face > baseline	colour detection of fixation cross	static colour	n/a	n/a	n/a	3
Pierce et al. (2004)	unfamiliar faces > baseline	gender discrimination	static greyscale	8	9	n/a	n/a
Scherf et al. (2015)	faces > houses, objects, scrambled	one-back	static colour	3	6	n/a	11
Schulte-Ruther et al. (2011)	face emotion > width	expression discrimination	static colour	5	9	1	3
Wang et al. (2004)	face matching > geometric form	expression matching	static greyscale	11	10	n/a	n/a
Weng et al. (2011)	sad, happy, neutral faces > baseline	gender discrimination	static colour	n/a	n/a	6	n/a
Whyte et al. (2016)	faces > objects	one-back	static greyscale	n/a	n/a	n/a	5
Zurcher et al. (2013)	Thatcher faces up > inverted (cue eyes)	Thatcherized face discrimination	static greyscale	53	56	3	n/a

Note. ASD = autism spectrum disorder; TD = typically developing; n/a = not available.

Table 2.5

Between-group contrasts associated with language and face processing

Contrast	X	Y	Z	SDM-*Z*	*P*	Voxels	Region	BA
Language								
ASD>TD	56	-58	4	1.66	0.0002	258	Right middle temporal gyrus	37, 21
	20	-78	44	1.39	0.0011	179	Right cuneus/precuneus	7, 19
	8	-36	40	1.28	0.0022	104	Right medial cingulate	23
	58	-38	32	1.28	0.0023	54	Right supramarginal gyrus	40, 48
TD>ASD	-48	20	2	-2.26	0.0000	3059	Left inf front/mid temp gyrus	45, 48
	-2	24	32	-1.73	0.0001	1010	Bilateral anterior cingulate	24, 32
	52	-26	-8	-1.23	0.0025	61	Right middle temporal gyrus	21
	-38	-38	-14	-1.17	0.0035	13	Left occipital temporal sulcus	NL
Face								
ASD>TD	-42	-78	22	1.91	0.0002	748	Left middle occipital gyrus	39, 19
	10	34	26	1.27	0.0027	122	Bilateral anterior cingulate	32, 24
	-10	16	-2	1.26	0.0028	105	Left striatum/caudate nucleus	25
	-58	-36	-2	1.17	0.0036	82	Left middle temporal gyrus	21
	30	22	46	1.15	0.0038	42	Right middle frontal gyrus	8, 9
TD>ASD	38	-52	-18	-2.63	0.0000	2536	Right fusiform gyrus	37, 19, 20
	-14	-98	2	-1.81	0.0002	745	Left calcarine fissure	17
	-20	4	-18	-1.94	0.0001	632	Left amygdala/insula	34, 48, 28
	50	-66	18	-1.63	0.0005	407	Right middle temporal gyrus	39, 37
	-30	-60	-14	-1.36	0.0024	75	Left fusiform gyrus	

Note. ASD = autism spectrum disorder; TD = typically developing; X/Y/Z = MNI coordinates; SDM-*Z* = seed-based differential mapping *Z*-score; Voxels = 2 mm^3; BA = Brodmann areas (BA are listed in order of highest to lowest SDM-*Z* value); inf front/mid temp = inferior frontal and middle temporal; NL = not listed.

Table 2.6

Cluster overlap from between-group contrasts

Contrast	Region	Voxels	X_{centre}	Y_{centre}	Z_{centre}	X_{max}	Y_{max}	Z_{max}
L: TD>ASD; F: ASD>TD	Left STS	58	-60	-32	0	-59	-35	3
L: TD>ASD; F: ASD>TD	Right ACC	29	4	29	32	4	26	39
F: TD>ASD; L: ASD>TD	Right STS	110	55	-59	5	56	-60	4

Note. F = face; L = language; ASD = autism spectrum disorder; TD = typically developing; STS = superior temporal sulcus; ACC = anterior cingulate cortex; Voxels = $2mm^3$; X/Y/Z = MNI coordinates; centre = centre of mass; max = maximum.

Table 2.7

Foci from within-group contrasts: Conjunction (ASD & TD)

Domain	X	Y	Z	Voxels	Region	BA
Language	-42	30	-14	9085	Left inf front/mid temp gyrus	47, 38, 21
	-2	14	40	1673	Bilateral superior frontal gyrus	24, 32
	60	-18	0	1582	Right superior temporal gyrus	48
Face	40	-64	-24	3045	Right fusiform gyrus	19, 37
	-42	-62	-16	2046	Left fusiform gyrus	37, 19

Note. ASD = autism spectrum disorder; TD = typically developing; X/Y/Z = MNI coordinates; Voxels = 2 mm^3; BA = Brodmann areas (BA are listed in order of highest to lowest SDM-*Z* value); inf front/mid temp = inferior frontal and middle temporal.

Table 2.8

Foci from within-group contrasts: Contrast analysis (ASD vs. TD)

Contrast	X	Y	Z	SDM-*Z*	*P*	Voxels	Region	BA
Language								
TD>ASD	8	20	48	-2.796	0.00000	1773	Bilat. superior frontal gyrus	32, 8, 24
Face								
TD>ASD	20	-2	-12	-2.002	0.00029	598	Right amygdala/insula	34
	48	-70	0	-1.878	0.00056	226	Right inferior occipital gyrus	37, 19
	50	20	2	-1.519	0.00302	31	Right inferior frontal gyrus	45

Note. ASD = autism spectrum disorder; TD = typically developing; X/Y/Z = MNI coordinates; SDM-*Z* = Seed-based d Mapping *Z*-score; Voxels = $2mm^3$; BA = Brodmann areas (BA are listed in order of highest to lowest SDM-*Z* value); bilat = bilateral.

Table 2.9

Foci from within-group contrasts: Domain conjunction (faces & language)

Group	X	Y	Z	Voxels	Label	BA
ASD	60	-48	8	119	Right middle/superior temporal gyrus	22
TD	n.s.					

Note. ASD = autism spectrum disorder; TD = typically developing; X/Y/Z = MNI coordinates; Voxels = $2mm^3$; BA = Brodmann areas; n.s. = not significant.

CHAPTER 3:

General Methods

3.1 Preface

The present general methods pertain to the following two chapters, entitled Task-Related Brain Activation (Chapter 4) and Intrinsic Functional Connectivity (Chapter 5).

3.2 Participants

Participants included 26 male ASD individuals and 25 male TD individuals who were all right-handed. The groups did not differ on mean age, IQ, and head motion parameters (p values > .10; ASD: age=21±4 years, IQ=115±11; TD: age=22±4 years, IQ=119±12). ASD participants were classified as high functioning, with an IQ over 70 (American Psychiatric Association, 2000). Data from 15 individuals in the TD group have been previously reported from orthogonal analyses (Stevens et al., 2015). ASD participants were assessed by an experienced clinician using the Autism Diagnostic Observation Schedule (ADOS) and met Diagnostic and Statistical Manual-IV (DSM-IV) diagnostic criteria for ASD (American Psychiatric Association, 2000). Written consent was obtained in accordance with a National Institutes of Health Institutional Review Board-approved protocol, and participants were monetarily compensated for their participation.

3.3 Functional Localizer

During fMRI scanning, participants performed 4 runs of a multi-category functional localizer task with a standard block-design, each run consisting of 14 task blocks (20 s) interleaved with 13 fixation blocks (10 s), with an additional fixation block at the beginning (18 s) and end (10 s) of the run. There were 14 different task block-types (1 of each block-type per run), consisting of 11 static image categories (i.e., animals, bodies, faces, scenes, tools, non-manipulable objects, abstract objects, scrambled objects, static dots, words, and written cues to move fingers and toes) and three dynamic image categories [i.e., dots moving in one of 4 directions, dots depicting biological motion (i.e., human bodies moving), and dots depicting non-biological motion (i.e., tools moving); Beauchamp et al., 2002, 2003]. Only seven block-types of interest were analyzed in this study: greyscale images (600 x 600 pixels) of faces (elliptically cropped to exclude hair and clothes; half female/half male), scenes (containing no animals or people), words (presented in different fonts), and nameable entities that comprised animals, body parts, common tools, and non-manipulable objects (Figure 3.1). Stimuli were matched in image-size to the longest dimension across all exemplars in all categories, projected onto a screen and viewed via a mirror mounted to the head coil.

Each task block included 20 trials (stimulus duration = 300 ms; interstimulus interval = 700 ms) of a category type with either 1 or 2 stimuli repeated in immediate succession in each block. To ensure attention to each stimulus,

participants performed a repetition detection (i.e., 1-back) task, by pressing a button with the left index finger to indicate a repetition. Each participant viewed at least 40 different exemplars in each of the four categories, with each exemplar repeated once throughout the entire experiment, either in immediate succession (only once or twice per block) or in separate runs.

3.4 fMRI Data Acquisition

MRI data were collected using a GE Signa 3 Tesla whole-body MRI scanner with an 8-channel head coil at the NIH Clinical Center NMR Research Facility (Bethesda, Maryland) using standard procedures. High-resolution T1-weighted anatomical images (MPRAGE) were collected for each participant (124 axial slices, slice thickness = 1.2 mm, field of view (FOV) = 24 cm, acquisition matrix = 256 x 256).

Spontaneously fluctuating brain activity was measured using gradient-echo echo-planar fMRI with whole-brain coverage during a “resting-state” run while participants lay still and rested quietly while maintaining visual fixation on a centrally located white cross on a grey background (repetition time (TR) = 3500 ms, echo time (TE) = 27 ms, flip angle = 90^{o}, 42 interleaved contiguous axial slices per volume, slice thickness = 3.0 mm, FOV = 220 mm, acquisition matrix = 128 x 128, single-voxel volume = 1.7 x 1.7 x 3.0 mm^{3}). Each resting-state run lasted 8 min 10 s (140 consecutive whole-brain volumes).

Next, task-evoked brain activity was similarly measured using fMRI during multiple runs of the task-based functional localizer. The task-based functional localizer (TR = 2000 ms, TE = 27 ms, flip angle = 77º, 41 interleaved contiguous axial slices per volume, slice thickness = 3.0 mm, FOV = 216 mm, acquisition matrix = 72 x 64, single-voxel volume = 3.0 mm isotropic) included four runs, each run lasting 7 min 18 s (219 consecutive whole-brain volumes). Independent measures of nuisance physiological variables (cardiac and respiration) were recorded during all scans for subsequent removal of noise-related artifacts.

3.5 fMRI Data Preprocessing

Echo-planar images were preprocessed using the Analysis of Functional Neuroimages (AFNI) software package (Cox, 1996). For each run, the first four image-volumes were removed. Large transients in the remaining volumes were removed through interpolation (3dDespike). Volumes were then slice-time corrected (3dTshift) and coregistered to the volume nearest the anatomical scan (3dVolreg). Nuisance physiological and non-physiological artifacts were removed using a modified version of the ANATICOR procedure (Jo et al., 2010; previously described in Stevens et al., 2015), which has been shown to drastically reduce motion-related artifacts in resting-state time-series analyses (Jo et al., 2013).

For ANATICOR, each participant's anatomical scan was segmented into tissue compartments using FreeSurfer (Fischl et al., 2002). Ventricle, white matter,

and draining-vessel masks were created and eroded to prevent partial volume effects with grey matter. These masks were applied to the volume-registered echo-planar image to generate nuisance time-series for the ventricles and draining-vessels, as well as local estimates of the white matter BOLD signal averaged within a 15 mm radius sphere. Regressors for cardiac activity and respiration were created using RETROICOR (Glover et al., 2000) and RetroTS in the AFNI Matlab library for respiration volume per time (RVT; Birn et al., 2008). Nuisance variables for each voxel's time-series included: an average ventricle time-series, an average draining-vessel time-series, a local average white matter time-series, six head motion parameter estimates and their temporal derivatives, and nine physiological signal regressors from RETROICOR and RVT. All of these nuisance time-series were detrended with fourth-order polynomials. Least-squares model fitted time-series of these nuisance variables were subtracted from the voxel time-series, generating a residual time-series used in all subsequent statistical analyses.

This modified ANATICOR procedure eschews temporal filtering (e.g., bandpass filtering), which is ineffective at removing signals with frequencies above the Nyquist frequency (i.e., 0.5 x 1/TR ≈ 0.143 Hz in this study) such as cardiac and respiratory signals (Gotts, Saad, et al., 2013; Van Dijk et al., 2010), as well as global signal regression, which can distort RSFC results in a number of detrimental ways (Gotts, Saad, et al., 2013; Murphy et al., 2009; Saad et al., 2012). Spatial smoothing was performed with 6 mm FWHM Gaussian blur (3dmerge).

Subject-specific cortical surface models were created from each participant's anatomical scan using FreeSurfer (Fischl, 2012) in order to facilitate ROI localization. Standard-mesh surfaces of 141,000 nodes per hemisphere were created using AFNI Surface Mapper (SUMA; Saad et al., 2004) to produce node-to-node anatomical correspondence across surfaces from multiple participants. The denoised residual time-series were mapped onto the cortical surfaces (3dVol2Surf), with a mean kernel of 10 sampling points uniformly distributed along a line between smooth white matter and pial surfaces, extending 80% of the distance between corresponding nodes on the two surfaces.

3.6 fMRI Data Analysis

To derive the BOLD response magnitudes for each of the conditions of interest at the individual subject level, the functional localizer data were modeled with a boxcar function, with the onset and offset points coinciding with the beginning and end of each task-block, respectively, convolved with a canonical hemodynamic response function and deconvolved using AFNI (3dDeconvolve –block). The model included 14 regressors corresponding to the 14 stimulus categories, in addition to nuisance regressors (12 regressors for the motion parameters and a third-order polynomial regressor to account for very low-frequency MRI signal drift). This analysis was conducted for both volume-based and surface-based localizer data.

3.7 ROI Definition

The localizer data were used to functionally define ROIs both at the group-level (i.e., averaged across all 51 participants) and in each individual participant, that were then applied to each participant's respective resting-state data for ROI-based RSFC analyses (Figure 3.2). ROI peak activations were identified in anatomically relevant regions and confirmed in standard atlases. ROI peak activation (*t*-statistic) locations were defined in both volume-based and surface-based space simultaneously, using spatially locked anatomically corresponding AFNI and SUMA viewing interfaces, to cross-reference activations across viewing modalities and facilitate anatomical specificity and accuracy.

A standard contrast of activation for faces versus scenes was used to identify key face- and scene-preferential regions. Face-preferential regions included: the posterior superior temporal sulcus (pSTS; Puce et al., 1998), "fusiform face area" (FFA) in the middle fusiform gyrus (Kanwisher et al., 1997), "occipital face area" (OFA) in the inferior occipital gyrus (Gautier et al., 2000), as well as the inferior frontal junction (Chan & Downing, 2011; Vignal et al., 2000), anterior temporal lobe (ATL; Collins & Olson, 2014), and amygdala (AMG; Young et al., 1995). Scene-preferential regions included: the "parahippocampal place area" (PPA) in parahippocampal cortex (Epstein & Kanwisher, 1998) and "occipital place area" (OPA) in the transverse occipital sulcus (Dilks et al., 2013).

A balanced contrast of activation for words versus nameable entities (i.e., animals, bodies, tools, and non-manipulable objects) was used to identify word-

and nameable entity-preferential regions. Word-preferential regions included: the "visual word form area" (VWFA) in ventral occipitotemporal cortex (Cohen et al., 2000), the posterior VWFA (pVWFA) in ventral occipital cortex (Dehaene & Cohen, 2011), Wernicke's area for speech comprehension (WERN) in the planum temporale of the superior temporal gyrus posterior to Heschl's gyrus (Wernicke, 1874), Broca's area for speech production (BROC) in the pars opercularis of the inferior frontal gyrus (Broca, 1861), and the precentral gyrus (PCG; Alexander et al., 1990). Nameable entity-preferential regions included: the lateral occipital complex (LOC) and posterior fusiform sulcus (Grill-Spector et al., 2001).

Individually defined ROI masks were created in each participant's native brain space. Group defined ROI masks were created in Montreal Neurological Institute (MNI) template space (i.e., MNI152_T1_2009c) with all 51 participants included. For each volume-based ROI, a sphere was created around the peak coordinate with a radius of 6 mm and all voxels that exceeded a threshold of $t > 0$ in the contrast of interest were included in the mask. All regions were localized bilaterally in native space for all participants (n = 51).

3.8 Statistical Analysis

Analyses were conducted in R: A language and environment for statistical computing (R Core Team, 2016; www.r-project.org). All *p* values were corrected

for multiple comparisons with the false discovery rate (FDR) procedure (Benjamini & Hochberg, 1995). Alpha was set at $p < .05$ for significance and $p < .10$ for trends.

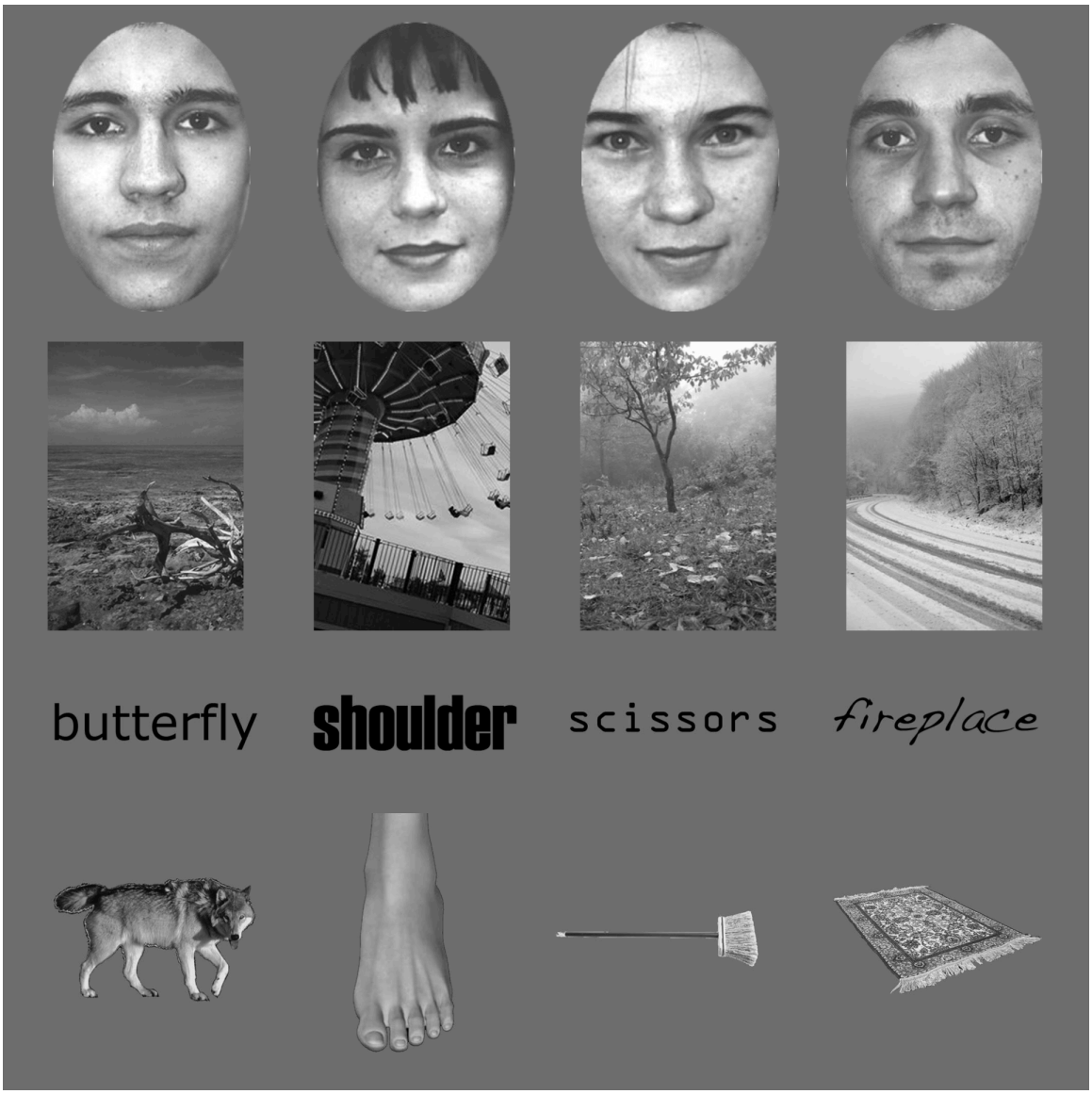

Figure 3.1. Example stimuli used in functional localizer task. Rows from top to bottom: 1) faces, 2) scenes, 3) words, and 4) nameable entities. Face- and scene-related regions were identified with a standard contrast of faces > scenes. Word- and nameable entity-related regions were identified with a balanced contrast of words > nameable entities (animals, bodies, tools, and non-manipulable objects).

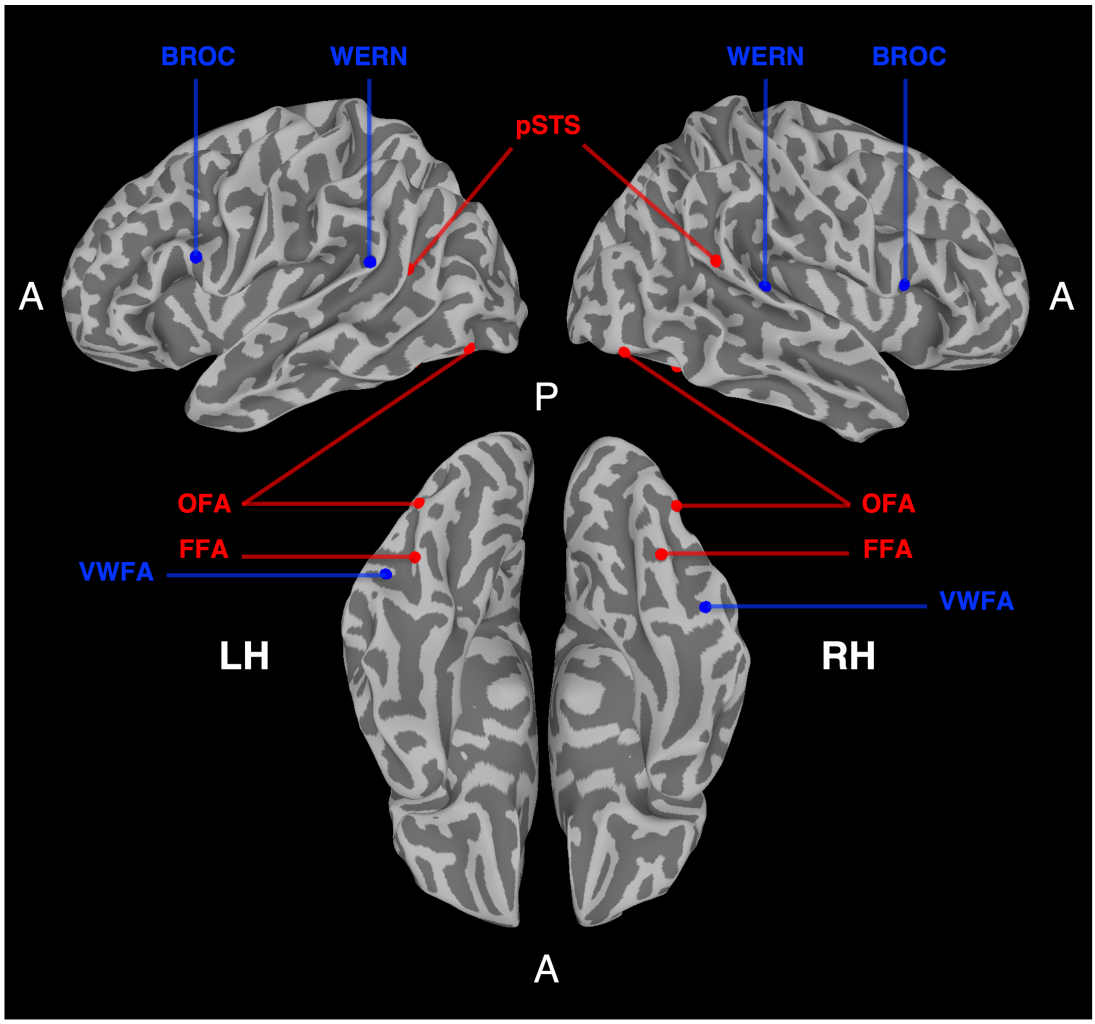

Figure 3.2. Lateral and ventral views of a cortical surface reconstruction with individually localized peaks of core face- (shown in red) and word- (shown in blue) related regions in a representative participant. A = anterior; P = posterior; LH = left hemisphere; RH = right hemisphere; *Face regions:* FFA = fusiform face area; OFA = occipital face area; pSTS = posterior superior temporal sulcus; *Word regions:* BROC = Broca's area; WERN = Wernicke's area; VWFA = visual word form area.

CHAPTER 4:

Task-Related Brain Activation

4.1 Abstract

The present chapter examined task-related brain activation in response to images of faces and words during a multi-category functional localizer in matched groups of high functioning ASD and TD participants, using both data-driven multivariate and hypothesis-driven univariate fMRI analysis techniques. Data-driven multivariate analyses (i.e., mean-centred partial least squares) indicated reduced functional specialization for processing faces and words in the ASD group. Hypothesis-driven univariate analyses (i.e., individually localized ROIs) indicated reduced hemispheric lateralization of activation in critical regions for processing these categories (i.e., reduced right hemisphere lateralization of activation for faces in the pSTS, and reduced left hemisphere lateralization of activation for words in the VWFA). Moreover, the degree of hemispheric lateralization for faces in the pSTS and for words in the VWFA were not significantly correlated with each other in the TD group, but they were significantly correlated in the ASD group, suggesting that there could be a similar underlying cause of disrupted lateralization of category-specific activation in these regions in ASD.

4.2 Introduction

Language and face processing are specialized cognitive domains that are critically important for skillful social interaction, which can often be challenging for autistic individuals. While the fMRI literature on autism indicates a lack of the typically observed left hemisphere specialization for language, the literature on face processing is less clear. One reason for disparate findings across studies is discrepancies in how ROIs are localized for fMRI analyses.

Although it is a tedious process, individual localization of ROIs in each participant is necessary to observe many existing findings in the literature, such as orthographic selectivity in the VWFA (Glezer & Riesenhuber, 2013; Stevens et al., 2017). While the general architecture of functional networks is strikingly similar across individuals, every brain is unique with its own individual differences. Using group-defined or literature-based coordinates to localize ROIs introduces noise that can completely negate effects observed in individually identified regions.

The aim of the present chapter was to examine face and word processing in matched groups of ASD and TD participants using individually localized ROIs. The hypotheses were as follows: ASD participants should show reduced functional specialization for processing faces and words in data-driven multivariate fMRI analyses, as well as reduced right hemisphere lateralization of activation for faces and reduced left hemisphere lateralization of activation for words in individually localized ROIs (i.e., hypothesis-driven univariate fMRI analyses). Finally, this reduced lateralization of category-preferential activation should be particularly

evident in the pSTS, as suggested by results from the quantitative fMRI meta-analyses reported in Chapter 2.

4.3 Methods

4.3.1 Preface

Details about the participants, functional localizer, fMRI data acquisition, fMRI data preprocessing, fMRI data analysis, ROI definition, and statistical analysis are detailed in Chapter 3, General Methods.

4.3.2 Univariate Whole-Brain Analysis

Functional localizer data were analyzed at the group level using voxel-wise *t*-tests (3dttest++ -Clustsim), which were controlled for multiple comparisons using randomization and permutation simulation to produce cluster-level threshold values in order to globally control the false positive rate. The cluster method employed was NN1 (i.e., faces must touch for neighbouring voxels to be considered part of the same cluster) bi-sided (i.e., both positive and negative t-values are included, but they do not cluster together). A voxelwise threshold of $p <$ .001 and cluster threshold of $p < .05$ was used. However, there were no significant whole-brain group differences in the examined contrasts (i.e., faces versus scenes, and words versus nameable entities).

4.3.3 Multivariate Whole-Brain Analysis

Multivariate fMRI analysis techniques lend themselves to connectionist theories of neurocognitive function, since they identify patterns of covariance of activity across brain regions, contrary to voxelwise univariate approaches that analyze the activity of each voxel independently. Partial least squares (PLS) is a multivariate technique for spatiotemporal analysis of fMRI data – i.e., patterns of covariance are analyzed across space and time together (McIntosh et al., 1996). This technique is based on the neural context hypothesis, which posits that the functional relevance of brain regions depends on the status of their connections with other areas, or the context within which a region is operating (McIntosh, 1999, 2000, 2004; McIntosh et al., 2001). This data-driven method identifies and separates significant covariance patterns into latent variables (LVs) and determines which conditions are driving each LV. PLS computes the optimal least squares fit to the correlation matrix between dependent measures (i.e., changes in BOLD signal) and exogenous variables (i.e., task performance or activity in other brain regions).

PLS refers to two different, but related methods. Symmetric PLS, or partial least squares correlation (PLSC), analyses information common to neural data and behaviour or experimental design. Asymmetric PLS, or partial least squares regression (PLSR), predicts behaviour or design from neural data. PLSC is more widely used in neuroimaging and exists in several forms, depending on the type of data being related to brain signal (Krishnan et al., 2011). For example, task PLSC

analyses how brain activity relates to the experimental design, while seed PLSC analyses the pattern of task-related functional connectivity between regions.

Here, mean-centred task PLSC analyses were performed on activation for faces and words in the functional localizer data. These analyses included permutation tests (500 permutations) to assess statistical significance of the latent variables, and a bootstrap resampling technique (500 bootstraps) to assess reliability of the latent variables across participants. The following mean-centred task PLSC analyses were performed: ASD versus TD group for face- versus word-related activation; ASD versus TD group for face-related activation only; ASD versus TD group for word-related activation only; face- versus word-related activation in the TD group only; and face- versus word-related activation in the ASD group only.

4.3.4 ROI Properties

Independent samples *t*-tests were performed on the location and size of individually defined ROIs identified to examine any differences in ROI properties between groups (Table 4.1).

4.3.5 Laterality Analysis

Linear mixed effect model analyses with Group (ASD versus TD) and Hemisphere (left versus right) as factors were performed to examine laterality effects in each ROI using the maximum log-likelihood method with *nlme* (Pinheiro

et al., 2017). Main effects of Group and Hemisphere, and the interaction between Group and Hemisphere were included in the analyses. Percent signal change (i.e., beta values) for the preferred stimulus category was modelled as a fixed effect, while participants and hemisphere were random effects. Diagnostics were performed on the residuals to assure that model assumptions were satisfied. *P* values were obtained by likelihood ratio tests of the full model with the effect in question against the model without it.

4.4 Results

4.4.1 PLS on Functional Localizer

Significant LVs were not observed in any of the group comparison analyses (i.e., ASD versus TD group for face- versus word-related activation, face-related activation only, or word-related activation only; p values > .10). However, when examining each group separately, the TD group showed a significant LV differentiating patterns of brain activation for faces versus words (p = .03, 100% variance accounted for; Figure 4.1), while the ASD group did not show a significant LV differentiating activation patterns for faces and words (p = .14, 100% variance accounted for; Appendix A, Figure A.1).

4.4.2 ROI Properties

The number, location, and size of all individually identified ROIs are indicated in Table 4.1. Most ROIs were successfully localized in all participants. Some participants in both the ASD and TD groups showed no significant face-related activation in the AMG bilaterally. However, the ASD group had more participants without face-related activation in the right (n = 6) than left (n = 4) AMG, while the TD group had more participants without face-related activation in the left (n = 4) than right (n = 2) AMG. Some participants in the TD group were also missing face-related activation in the IFJ bilaterally. However, there were more TD participants without face-related activation in the left (n = 2) than right (n = 1) IFJ. Finally, one ASD participant was missing nameable entity-related activation in the left LOC. Notably, the TD group had more participants without left than right hemisphere face-related regions, which was to be expected since face processing is typically right hemisphere dominant. However, the ASD group had more participants without right than left hemisphere face-related regions.

There were no statistically significant group differences in ROI locations when tests were corrected for multiple comparisons (FDR) across all ROIs. However, when comparisons were FDR-corrected for only the x, y, and z coordinates per each ROI, the following differences were observed (the following mean values refer to the mean group difference in the location of the peak in mm): left FFA in the x [M = -4.21 (-7.77, -.66), t(49) = -2.38, p = .04] and z [M = -2.92 (-5.52, -.32), t(48) = -2.26, p = .04] planes; right AMG in the x plane [M = 4.48 (1.37,

7.58), $t(33) = 2.94$, $p = .02$]; left WERN in the x plane [$M = -4.30$ (-7.82, -.78), $t(43) = -2.46$, $p = .05$]; and left VWFA in the y plane [$M = 7.55$ (1.22, 13.87), $t(45) = 2.40$, $p = .06$].

There were also no statistically significant group differences in ROI sizes when tests were corrected for multiple comparisons (FDR) across all ROIs. However, without correction for multiple comparisons, the following differences were observed (the following mean values refer to the mean group difference in ROI size, where size is the number of voxels exceeding $t > 0$ in the relevant contrast within a 6 mm radius sphere): the left pSTS was larger in the ASD than TD group [$M = 1.77$ (.09, 3.44), $t(35) = 2.14$, $p = .04$ uncorrected], while the right IFJ [$M = -1.24$ (-2.51, .03), $t(45) = -1.97$, $p = .06$ uncorrected] and right ATL [$M = -1.70$ (-3.44, .04), $t(49) = -1.96$, $p = .06$ uncorrected] were marginally larger in the TD than ASD group. Notably, the TD group showed marginally larger face-related ROIs in the right hemisphere, while the ASD group showed a marginally larger face-related ROIs in the left hemisphere.

4.4.3 Laterality of Task-Related Activation

The interaction between Group and Hemisphere marginally improved model fit for face-related activation in the individually defined pSTS [$\chi^2(1) = 3.16$, $p = .07$, $b = .09$, $SE_b = .05$]. Due to the directional *a priori* hypothesis regarding this marginal interaction based on the results of the meta-analysis in Chapter 2, a one-tailed *t*-test was also performed on the difference in face-related activation between the

right and left pSTS, which demonstrated a significant group difference [$t(48) = -1.77$, $p = .04$]. Two-tailed pairwise comparisons revealed that the TD group had higher activation for faces in the right than the left pSTS [$M = -.08$ (-.16, -.001), $t(24) = -2.09$, $p = .04$], while there was no hemispheric difference in the ASD group [$M = .009$ (-.06, .08), $t(25) = .27$, $p = .79$] (Figure 4.2). This interaction was not observed for word-related activation in the individually defined pSTS [$\chi^2(1) = .19$, $p = .66$] (Figure 4.4). The interaction between Group and Hemisphere for face-related activation was more highly significant in the group-level pSTS than that in the individually defined ROIs [$\chi^2(1) = 5.36$, $p = .02$, $b = .11$, $SE_b = .05$] (Figure 4.3). However, the overall amplitude of face-related activation was significantly higher in the individually defined bilateral pSTS ($M = .22$) compared to the group-level ROIs ($M = .03$), supporting the usefulness of individual localization [$t(193) = 8.33$, $p < .001$].

The interaction between Group and Hemisphere significantly improved model fit for word-related activation in the individually defined VWFA [$\chi^2(1) = 7.30$, $p = .007$, $b = -.32$, $SE_b = .11$] (Figure 4.2). Pairwise comparisons revealed that the TD group had higher activation for words in the left than the right VWFA [$M = .38$ (.18, .58), $t(24) = 3.93$, $p < .001$], while there was no hemispheric difference in the ASD group [$M = .06$ (-.06, .19), $t(25) = 1.03$, $p = .31$]. This interaction was not observed for face-related activation in the individually defined VWFA [$\chi^2(1) = 1.49$, $p = .22$] (Figure 4.4), nor was it observed for word-related activation in the group-

level VWFA [$\chi^2(1) = 1.42$, $p = .23$], highlighting the importance of individual localization (Figure 4.3).

The main effect of Hemisphere marginally improved model fit for face-related activation in the individually defined FFA [$\chi^2(1) = 3.62$, $p = .05$, $b = .08$, $SE_b = .04$], indicating higher overall face activation in the right than the left FFA across participants. The main effect of Hemisphere significantly improved model fit in the individually defined IFJ [$\chi^2(1) = 6.12$, $p = .01$, $b = .07$, $SE_b = .03$], indicating higher overall face activation in the right than the left IFJ. The main effect of Hemisphere also significantly improved model fit for word-related activation in the individually defined BROC [$\chi^2(1) = 23.13$, $p < .001$, $b = -.10$, $SE_b = .02$], indicating higher overall word activation in the left than the right BROC across participants. There were no other differences in category-related brain activation (ps > .10).

Since the pSTS and VWFA were the only individually localized ROIs to show interactions of interest between Group and Hemisphere for category-preferential activation, the relationship between the lateralization of activation in these regions was examined with a Pearson correlation (Figure 4.5). The correlation between face activation in the right - left pSTS and word activation in the left - right VWFA was significant in the combined groups overall ($r = .34$, $p = .01$). However, when the groups were examined separately, the correlation between face lateralization in the pSTS and word lateralization in the VWFA was only significant in the ASD group ($r = .57$, $p = .002$) and not in the TD group ($r = .11$, $p = .61$). The difference in correlations was also significant ($z = 2.44$, $p = .007$).

4.5 Discussion

The present work examined task-related brain activation in response to images of faces and words during a multi-category functional localizer, using both data-driven multivariate and hypothesis-driven univariate analysis techniques. The data-driven multivariate analyses indicated decreased functional specialization for processing faces and words in the ASD group, while the hypothesis-driven univariate analyses indicated decreased hemispheric lateralization of activation in critical regions for processing these categories.

The mean-centred PLS analyses of task-related fMRI data indicated decreased specialization for processing faces and words in ASD. While the TD group demonstrated a significant LV differentiating spatiotemporal covariance patterns related to faces and words, the ASD group did not. There was also no coherent covariance pattern differentiating categories when looking at both conditions in both groups, further indicative of decreased specialization for processing these categories in ASD.

The significant LV differentiating faces and words in the TD group showed spatial patterns reflective of classical face and language networks, respectively (Figure 4.1). As expected, the spatiotemporal pattern associated with words was predominantly observed in the left hemisphere, while the pattern associated with faces was predominantly observed in the right hemisphere. Notably, word-related regions included the left inferior frontal gyrus (i.e., putative Broca's area), left planum temporale (i.e., putative Wernicke's area), left ventral occipitotemporal

cortex (i.e., putative VWFA), and left precentral gyrus. Face-related regions were observed bilaterally with a clear right hemisphere dominance. They included the pSTS, amygdala, lateral fusiform gyrus (i.e., putative FFA), and inferior occipital gyrus (i.e., putative OFA).

The univariate analyses of brain activation for faces and words in individually localized ROIs indicated that the ASD group showed reduced hemispheric lateralization in two important regions for processing these categories: reduced rightward lateralization of the pSTS for faces and leftward lateralization of the VWFA for words (Figure 4.2). Decreased lateralization of activation in these regions was category specific, such that significant group differences were not observed for faces in the VWFA or for words in the pSTS (Figure 4.4). Nonetheless, word activation in the pSTS showed the expected pattern, where the TD group demonstrated higher activation for words in the left than the right pSTS, while no hemispheric difference was observed in the ASD group. This suggested that reduced hemispheric specialization for processing faces and words in autism may be particularly evident in the pSTS.

The pSTS is an area of particular importance as it has been implicated in many previous studies of autism (e.g., Kana et al., 2014; Levitt, 2003; Pelphrey et al., 2011; Saitovitch et al., 2012; Shih et al., 2011), while the VWFA is particularly relevant to the present work since participants were presented with visual words. The pSTS was also implicated by the quantitative fMRI meta-analysis outlined in Chapter 2, which found a region in the right pSTS that was consistently related to

both language and face processing in ASD participants across studies, while no such regions were observed in TD participants. The meta-analysis in Chapter 2 also found regions in the bilateral STS that were associated with the expected domain in TD groups (i.e., language in the left hemisphere and face processing in the right hemisphere) and the opposite domain in ASD groups (i.e., language in the right hemisphere and face processing in the left hemisphere).

Interestingly, the level of hemispheric lateralization for faces in the pSTS and for words in the VWFA were not significantly correlated with each other in the TD group, but they were significantly correlated in the ASD group (Figure 4.5). This finding suggested that there could be a similar underlying cause of reduced lateralization of category-specific activation in the pSTS and VWFA in autism.

The present results further indicated the critical importance of individual localization of ROIs in each participant. There was no significant interaction between Group and Hemisphere for word-related activation in the group-level VWFA (Figure 4.3), hence individual localization was necessary to observe this result. While the interaction between Group and Hemisphere was more highly significant in the group-level pSTS, the overall amplitude of face-related activation was substantially higher in the individually localized pSTS, which further supported the importance of individual localization.

Taken together, the present findings were aligned with the hypotheses that ASD participants would demonstrate reduced specialization for processing faces and words (i.e., PLS results), as well as reduced right hemisphere lateralization of

activation for faces and reduced left hemisphere lateralization of activation for words (i.e., univariate results), and that reduced lateralization of category-preferential activation would be particularly evident in the pSTS (i.e., univariate results). Future work should examine whether these activation differences simply reflect disparate cognitive strategies in processing words and faces, or whether reduced lateralization of critical regions involved in language and face processing is an intrinsic property of functional network architecture in ASD. This is investigated in the following chapter.

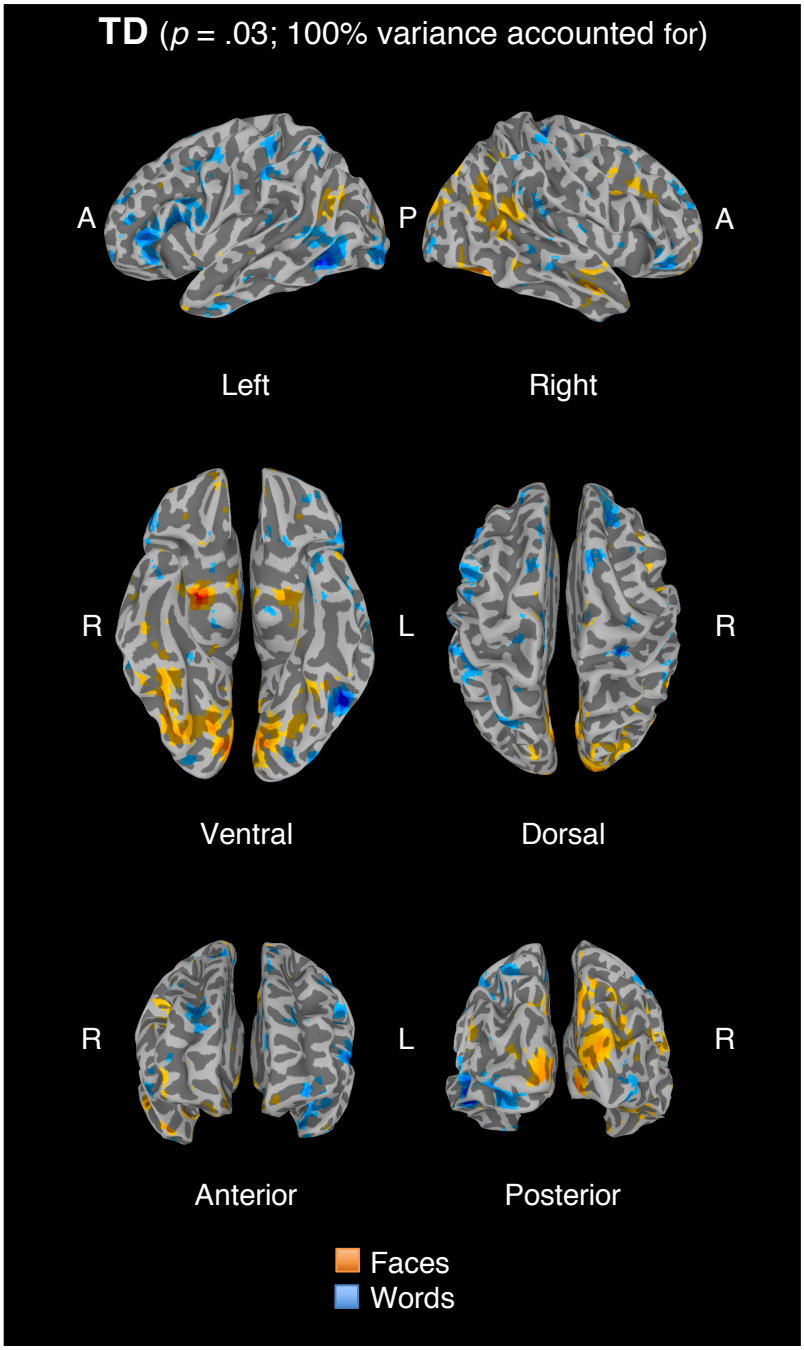

Figure 4.1. Spatiotemporal patterns of brain activation in response to faces (warm colours) and words (cool colours) from mean-centred partial least squares (PLS) analysis. TD = typically developing; A = anterior; P = posterior; L = left; R = right.

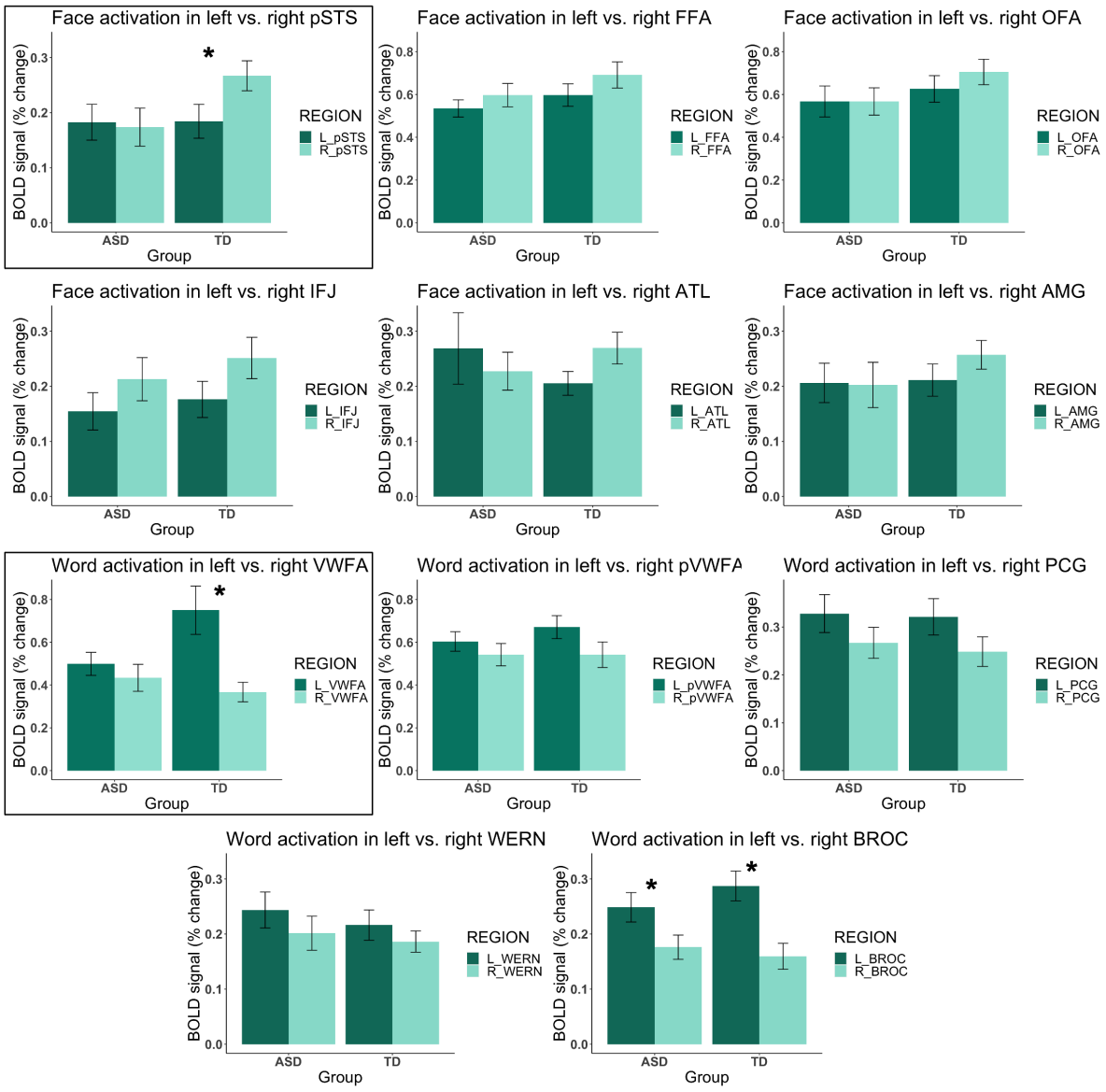

Figure 4.2. Laterality of category-preferential activation in individually localized face-related (top two rows) and word-related (bottom two rows) regions. Panels with a significant Group x Hemisphere interaction are indicated with rectangular outlines. ASD = autism spectrum disorder; TD = typically developing; BOLD = blood-oxygen-level-dependent; L = left; R = right; *Face regions:* FFA = fusiform face area; OFA = occipital face area; pSTS = posterior superior temporal sulcus; IFJ = inferior frontal junction; ATL = anterior temporal lobe; AMG = amygdala; *Word*

regions: VWFA = visual word form area; pVWFA = posterior VWFA; WERN = Wernicke's area; BROC = Broca's area; PCG = precentral gyrus; * = $p < .05$.

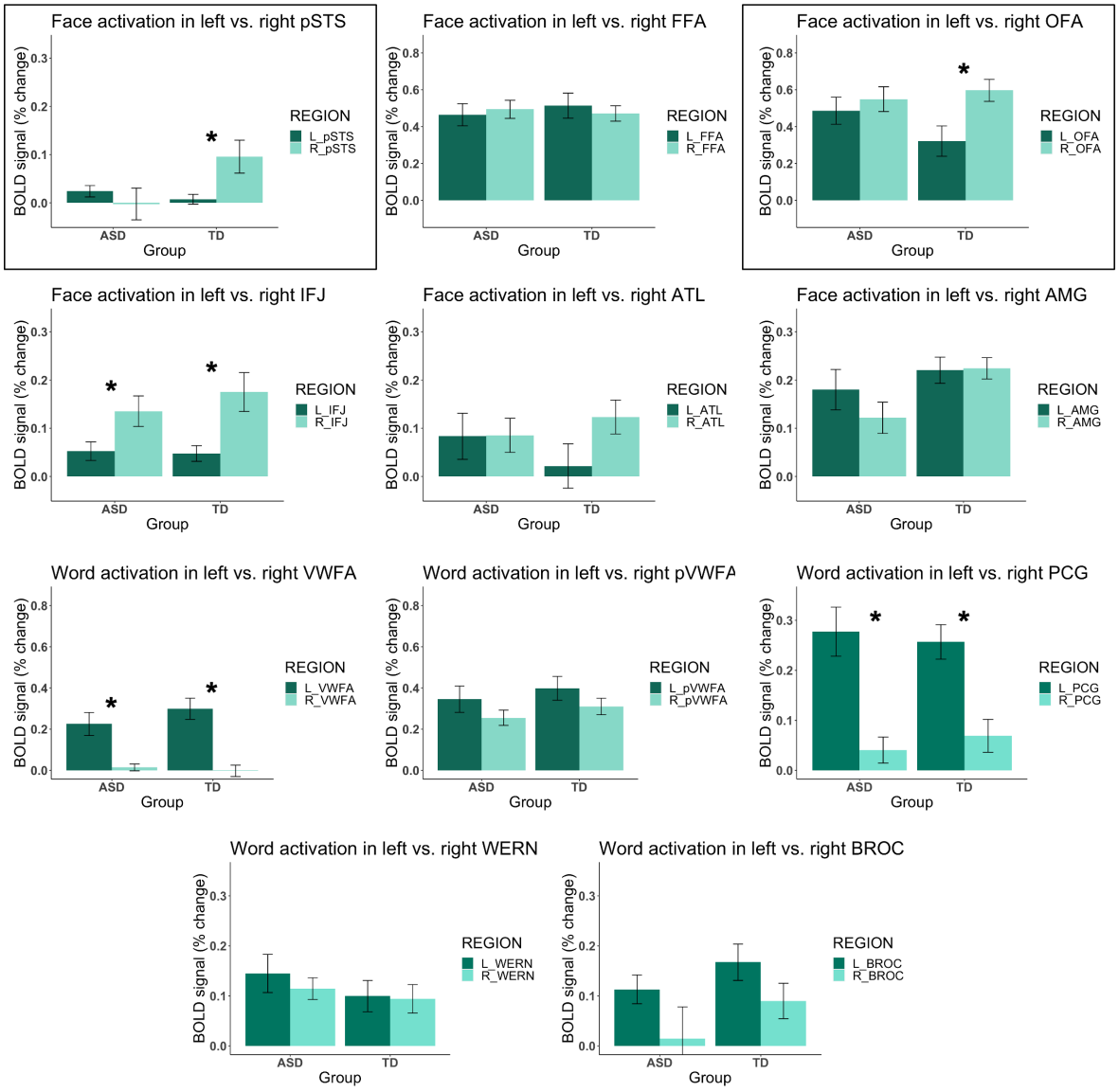

Figure 4.3. Laterality of category-preferential activation in group-defined face-related (top two rows) and word-related (bottom two rows) regions. Panels with a significant Group x Hemisphere interaction are indicated with rectangular outlines. ASD = autism spectrum disorder; TD = typically developing; BOLD = blood-oxygen-level-dependent; L = left; R = right; *Face regions:* FFA = fusiform face area; OFA = occipital face area; pSTS = posterior superior temporal sulcus; IFJ = inferior frontal junction; ATL = anterior temporal lobe; AMG = amygdala; *Word regions:*

VWFA = visual word form area; pVWFA = posterior VWFA; WERN = Wernicke's area; BROC = Broca's area; PCG = precentral gyrus; * = $p < .05$.

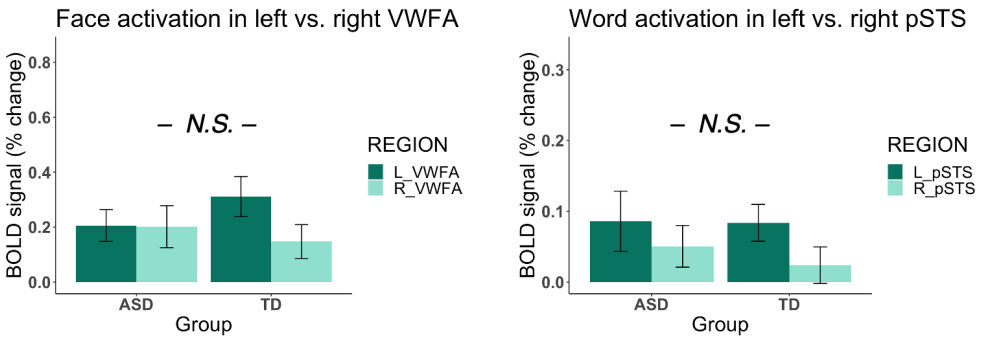

Figure 4.4. Face-related activation in the individually localized visual word form area (VWFA) and word-related activation in the individually localized posterior superior temporal sulcus (pSTS). There were no significant interactions in activation for non-preferred categories. ASD = autism spectrum disorder; TD = typically developing; BOLD = blood-oxygen-level-dependent; L = left; R = right; N.S. = not significant.

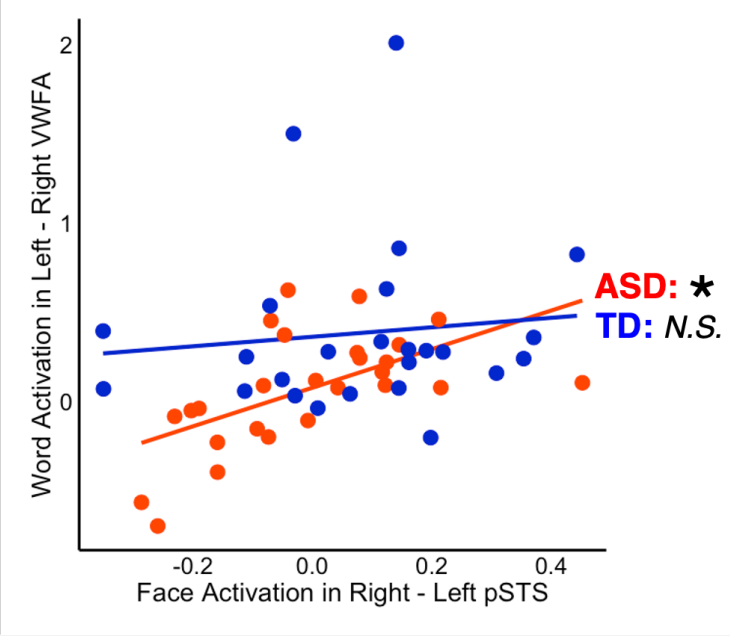

Figure 4.5. The Pearson correlation between left minus right hemisphere activation for words in the individually localized visual word form area (VWFA) and right minus left hemisphere activation for faces in the individually localized posterior superior temporal sulcus (pSTS) was significant in the ASD group (r = .57, p = .002; shown in red), but not in the TD group (r = .11, p = .61; shown in blue). The difference in correlations was also significant (z = 2.44, p = .007). ASD = autism spectrum disorder; TD = typically developing; * = $p < .05$; N.S. = not significant.

Table 4.1

Number of individual ROIs identified and their mean (SD) size and location per group

ROI	ASD (n = 26)					TD (n = 25)					Size *p* (uncorr.)
	N	Voxels	X	Y	Z	N	Voxels	X	Y	Z	
Faces > scenes											
L pSTS	26	30.85 (1.85)	-52.15	-49.81	8.23	25	29.08 (3.70)	-49.64	-50.08	10.76	**0.04**
R pSTS	26	30.04 (1.89)	49.88	-48.81	9.04	25	30.28 (1.95)	49.20	-47.00	9.32	0.65
L FFA	26	29.96 (1.71)	**-41.69**	-44.62	**-25.04**	25	29.76 (2.28)	**-37.48**	-47.36	**-22.12**	0.72
R FFA	26	30.19 (1.10)	40.42	-44.92	-24.04	25	30.44 (1.96)	38.76	-44.32	-23.32	0.58
L OFA	26	31.04 (1.82)	-39.77	-74.00	-16.27	25	30.32 (1.82)	-36.32	-72.64	-17.28	0.16
R OFA	26	30.31 (1.64)	36.65	-76.23	-15.88	25	30.44 (1.39)	37.48	-72.36	-17.28	0.76
L IFJ	26	31.00 (2.65)	-41.27	22.04	18.27	**23**	31.58 (2.64)	-42.96	17.30	17.65	0.44
R IFJ	26	30.44 (1.89)	45.50	18.62	16.92	**24**	31.68 (2.51)	44.63	15.83	18.04	**0.06**
L ATL	26	30.23 (3.06)	-34.19	4.31	-36.12	25	29.68 (3.16)	-36.36	0.44	-34.08	0.53
R ATL	26	29.46 (3.15)	35.31	4.65	-39.12	25	31.16 (3.02)	31.48	3.40	-38.12	**0.06**

Table 4.1 (continued)

Number of individual ROIs identified and their mean (SD) size and location per group

ROI	ASD (n = 26)					TD (n = 25)					Size *p* (uncorr.)
	N	Voxels	X	Y	Z	N	Voxels	X	Y	Z	
Faces > scenes											
L AMG	**22**	29.82 (2.17)	-20.91	-0.95	-17.50	**21**	29.57 (2.44)	-20.00	-0.71	-16.95	0.73
R AMG	**20**	30.41 (3.44)	**26.00**	-0.65	-18.05	**23**	29.48 (3.61)	**21.52**	-1.04	-16.39	0.39
Words > nameable entities											
L VWFA	26	30.54 (2.76)	-41.19	**-47.69**	-19.15	25	29.60 (1.61)	-42.56	**-55.24**	-18.80	0.14
R VWFA	26	29.23 (2.85)	42.19	-49.77	-22.35	25	29.40 (3.18)	40.36	-57.28	-20.40	0.84
L pVWFA	26	31.38 (1.86)	-31. 50	-80.54	-15.35	25	31.48 (2.02)	-29.96	-82.80	-16.32	0.86
R pVWFA	26	31.00 (3.08)	29.38	-82.92	-11.85	25	31.24 (2.77)	30.64	-83.00	-15.16	0.77
L WERN	26	30.19 (3.08)	**-56.42**	-39.12	13.77	25	30.44 (2.87)	**-52.12**	-39.04	14.32	0.77
R WERN	26	30.96 (2.71)	54.31	-39.77	16.88	25	30.96 (3.22)	54.20	-36.56	13.56	1
L BROC	26	30.42 (2.79)	-45.65	16.35	15.62	25	30.40 (2.48)	-48.52	17.36	16.16	0.98
R BROC	26	29.42 (3.91)	47.12	17.38	13.62	25	31.16 (3.45)	48.52	16.04	13.68	0.10

Table 4.1 (continued)

Number of individual ROIs identified and their mean (SD) size and location per group

ROI	ASD (n = 26)					TD (n = 25)					Size *p* (uncorr.)
	N	Voxels	X	Y	Z	N	Voxels	X	Y	Z	
Words > nameable entities											
L PCG	26	30.08 (4.73)	-45.85	-6.46	42.65	25	31.08 (2.89)	-45.36	-8.60	45.36	0.36
R PCG	26	30.58 (3.57)	42.23	-7.92	45.38	25	31.72 (2.37)	43.24	-13.36	48.16	0.18
Scenes > faces											
L PPA	26	30.69 (1.35)	-29.08	-41.85	-12.08	25	30.52 (1.19)	-30.00	-40.04	-12.96	0.63
R PPA	26	30.58 (1.17)	27.12	-39.54	-15.23	25	30.96 (1.40)	27.08	-40.36	-14.76	0.30
L OPA	26	30.77 (0.91)	-29.88	-83.81	13.15	25	30.68 (0.94)	-30.88	-80.68	16.24	0.73
R OPA	26	30.65 (1.81)	32.50	-80.65	15.19	25	30.76 (1.33)	32.40	-81.52	15.52	0.81
Nameable entities > words											
L LOC	25	30.68 (1.44)	-40.76	-73.32	-2.40	25	30.72 (0.98)	-36.76	-73.72	-4.56	0.91
R LOC	26	31.31 (1.72)	38.31	-74.92	-2.69	25	31.52 (2.34)	35.80	-73.28	-5.36	0.71

Table 4.1 (continued)

Number of individual ROIs identified and their mean (SD) size and location per group

ROI	ASD (n = 26)					TD (n = 25)					Size *p* (uncorr.)
	N	Voxels	X	Y	Z	N	Voxels	X	Y	Z	
Nameable entities > words											
L pFS	26	29.88 (2.05)	-29.62	-54.50	-19.65	25	30.72 (1.81)	-29.64	-51.20	-18.08	0.13
R pFS	26	30.58 (2.18)	30.81	-54.85	-20.23	25	31.52 (1.92)	29.92	-52.56	-19.60	0.11

Note. Total number of participants per group = 26 (ASD = autism spectrum disorder) and 25 (TD = typically developing); ROI = region of interest; SD = standard deviation; N = number of participants (bolded when missing participants); L = left; R = right; X/Y/Z = Montreal Neurological Institute (MNI) coordinate of peak activation (beta-weight); Size *p* = group difference in number of voxels; uncorr. = uncorrected for multiple comparisons; pSTS = posterior superior temporal sulcus; FFA = fusiform face area; OFA = occipital face area; IFJ = inferior frontal junction; ATL = anterior temporal lobe; AMG = amygdala; VWFA = visual word form area; pVWFA = posterior VWFA; WERN = Wernicke's area; BROC = Broca's area; PCG = precentral gyrus; PPA = parahippocampal place area; OPA = occipital place area; LOC = lateral occipital complex; pFS = posterior fusiform sulcus. Coordinates with marginal group differences [false discovery rate (FDR) corrected $p < .07$] are bolded. No size differences survived FDR correction.

Table 4.2

Location of group-level ROIs

Contrast	Region of interest (ROI)	X	Y	Z
Faces > scenes				
	Left posterior superior temporal sulcus (pSTS)	-41	-53	10
	Right posterior superior temporal sulcus (pSTS)	58	-45	13
	Left fusiform face area (FFA)	-44	-59	-20
	Right fusiform face area (FFA)	40	-59	-14
	Left occipital face area (OFA)	-50	-77	-11
	Right occipital face area (OFA)	37	-74	-14
	Left inferior frontal junction (IFJ)	-41	16	19
	Right inferior frontal junction (IFJ)	43	10	22
	Left anterior temporal lobe (ATL)	-41	-14	-38
	Right anterior temporal lobe (ATL)	25	-8	-41
	Left amygdala (AMG)	-20	-5	-14
	Right amygdala (AMG)	22	-5	-14
Words > nameable entities				
	Left visual word form area (VWFA)	-53	-56	-14
	Right visual word form area (VWFA)	56	-37	-13
	Left posterior VWFA (pVWFA)	-32	-92	-14
	Right posterior VWFA (pVWFA)	22	-89	-5
	Left Wernicke's area (WERN)	-58	-47	9
	Right Wernicke's area (WERN)	52	-35	4
	Left Broca's area (BROC)	-47	13	22
	Right Broca's area (BROC)	52	28	-8
	Left precentral gyrus (PCG)	-53	-5	49
	Right precentral gyrus (PCG)	53	-6	43
Scenes > faces				
	Left parahippocampal place area (PPA)	-29	-44	-11
	Right parahippocampal place area (PPA)	25	-44	-11
	Left occipital place area (OPA)	-35	-86	25
	Right occipital place area (OPA)	37	-83	25
Nameable entities > words				
	Left lateral occipital complex (LOC)	-43	-79	13
	Right lateral occipital complex (LOC)	49	-69	-9
	Left posterior fusiform sulcus (pFS)	-32	-50	-11
	Right posterior fusiform sulcus (pFS)	28	-53	-11

Note. X/Y/Z = MNI coordinate of peak activation (beta-weight). All voxels within a 6 mm radius sphere around the peak were positively activated ($t > 0$) in the relevant contrast.

CHAPTER 5:

Intrinsic Functional Connectivity

5.1 Abstract

Here, resting-state fMRI was used to examine whether reduced functional specialization and/or reduced lateralization of critical regions involved in language and face processing is an intrinsic property of functional network architecture in ASD. Data-driven multivariate analyses (i.e., multidimensional scaling and *k*-means clustering) indicated decreased functional specialization of word processing regions (i.e., VWFA and pVWFA) in the ASD group, while hypothesis-driven univariate analyses (i.e., laterality indices) indicated atypical hemispheric lateralization of RSFC between two critical regions for processing words (i.e., BROC and VWFA) as well as between all three core face network regions (i.e., pSTS, FFA, and OFA). This is an important contribution to the mixed literature on face processing in ASD. While converging evidence has previously established reduced leftward lateralization of the language system in ASD, individual localization was necessary to observe the present findings in the face network. These results indicate that reduced lateralization of language and face processing is an intrinsic property of functional network architecture in ASD, rather than simply reflective of the use of different cognitive processing strategies during fMRI tasks.

5.2 Introduction

The quantitative fMRI meta-analysis reported in Chapter 2 found that ASD is related to atypical hemispheric specialization of both language and face processing, particularly in posterior lateral temporal cortex, i.e., the pSTS. The category-related task-based fMRI analyses in Chapter 4 found reduced functional specialization for processing faces and words in the ASD group, as well as reduced hemispheric lateralization of activation in critical regions for processing these categories (i.e., reduced rightward lateralization of face-related activation in the pSTS, and reduced leftward lateralization of word-related activation in the VWFA). However, the question remains regarding whether these group differences in brain activation reflect intrinsic differences in functional network architecture, or if they simply reflect different cognitive strategies used during fMRI tasks.

The aim of the present chapter was to examine whether reduced functional specialization and/or reduced lateralization of critical regions involved in language and face processing is an intrinsic property of functional network architecture in ASD using RSFC of resting-state fMRI data in individually localized ROIs. The hypotheses were as follows: ASD participants should show reduced functional specialization of critical regions for processing faces and words using multidimensional scaling and *k*-means clustering (i.e., data-driven multivariate analyses), as well as reduced right hemisphere lateralization of RSFC between face regions and reduced left hemisphere lateralization of RSFC between word regions (i.e., hypothesis-driven univariate analyses) in individually localized, but

not group-level, ROIs. Finally, this reduced lateralization of RSFC should be particularly evident in the pSTS, as suggested by the results reported in Chapters 2 and 4.

5.3 Methods

5.3.1 Preface

Details about the participants, functional localizer, fMRI data acquisition, fMRI data preprocessing, fMRI data analysis, ROI definition, and statistical analysis are outlined in Chapter 3, General Methods.

5.3.2 Resting-State Functional Connectivity

RSFC analyses were conducted in volume space. To preserve the integrity, specificity, and high spatial resolution of the resting-state data, the localizer data were aligned and resampled to the resolution of the resting-state data prior to analyses. Residual denoised BOLD signal time-series were extracted from the resting-state data by averaging across all voxels within the ROI masks to produce a single mean time-series for each ROI. Pairwise correlations (Pearson's *r*) between ROI time-series were calculated and transformed using Fisher's *z* prior to being analyzed at the group-level.

5.3.3 Multidimensional Scaling and *K*-means Clustering

Multidimensional scaling (MDS) is a data-driven method of visualizing the amount of similarity between items in a dataset, where more dissimilar items are father apart in what is termed a proximity matrix. MDS maps the pairwise distances among items into a configuration of points in abstract Cartesian space (Hout et al., 2013). Classical MDS, or principal coordinates analysis, takes an input matrix of dissimilarities between item pairs and outputs a coordinate matrix where the configuration minimizes a loss function termed strain (Gower, 1966, 2005).

K-means clustering is a method of grouping *n* observations into *k* clusters, where each observation is assigned to the cluster with the nearest mean (MacQueen, 1967). The elbow method is a means of determining the optimal number of clusters, where the within-cluster sum of squares (WSS) is calculated for different values of *k*, and the optimal *k* is chosen when the WSS starts to diminish, called the elbow point. Here, the elbow method demonstrated that four clusters accounted for the most variance without overfitting the data in both groups (Figure 5.1).

5.3.4 Laterality Analysis

Linear mixed effect model analyses with Group (ASD versus TD) and Hemisphere (left versus right) as factors were performed to examine laterality effects of RSFC between core regions of the face perception network (i.e., pSTS, FFA, and OFA; Haxby et al., 2000) using the PPA as a control region for

comparison, as well as core language network regions (i.e., Broca's area, Wernicke's area, and VWFA) using the LOC as a control region for comparison. These control regions were chosen since they were defined with the same contrast as the respective experimental regions (i.e., faces versus scenes, and words versus nameable entities). Main effects of Group and Hemisphere, and the interaction between Group and Hemisphere were included in the analysis. RSFC of the seed with the target of interest was entered into the model as a fixed effect, while subjects and hemisphere were random effects. Diagnostics were performed on the residuals to assure that model assumptions were satisfied. *P* values were obtained by likelihood ratio tests of the full model with the effect in question against the model without it. Significant effects were followed up with *t*-tests for pairwise comparisons, corrected for multiple comparisons with the FDR method.

Laterality indices were also calculated for RSFC between bilateral seed and target regions. Previous work has demonstrated two forms of functional lateralization in the brain (Gotts, Jo, et al., 2013): between-hemisphere interactions were termed "integration" [LL + LR – (RR + RL)], and within-hemisphere interactions were termed "segregation" [LL – LR – (RR – RL)], where LL is RSFC between the left seed and left target, RR is RSFC between the right seed and right target, LR is RSFC between the left seed and right target, and RL is RSFC between the right seed and left target (Gotts, Jo, et al., 2013). Positive integration and segregation scores are indicative of leftward lateralization, while negative scores are indicative of rightward lateralization. Integration is comparable to the single

laterality index used in other prior work (Liu et al., 2009), and thus, was chosen as the laterality index of choice in the present work. Group differences in integration scores were examined in one-way *t*-tests because the present hypotheses are directional (i.e., the TD group will show more strongly right lateralized RSFC between face-related regions, and more strongly left lateralized RSFC between word-related regions, compared to the ASD group).

5.4 Results

5.4.1 Multidimensional Scaling and *K*-means Clustering

In the TD group, intrinsic functional connectivity between all the individually localized ROIs grouped into the following clusters (Figure 5.2): cluster 1 included the bilateral pSTS, IFJ, PCG, BROC, and WERN; cluster 2 included the bilateral OFA, FFA, PPA, OPA, LOC, and pFS; cluster 3 included the bilateral AMG and ATL; and cluster 4 included the bilateral VWFA and pVWFA. In the ASD group, clusters 1 and 3 included the same regions as those observed in the TD group (outlined above). However, clusters 2 and 4 differed from the TD group. In the ASD group, cluster 2 included the bilateral OFA, OPA, LOC, and pFS, while cluster 4 included the bilateral PPA, FFA, VWFA, and pVWFA.

5.4.2 Laterality of Intrinsic Functional Connectivity

The interaction between Group and Hemisphere significantly improved model fit for connectivity between the individually defined right and left pSTS with the right FFA [$\chi^2(1) = 6.78$, $p = .009$, $b = .16$, $SE_b = .06$] (Figure 5.3). Pairwise comparisons revealed that the TD group showed significantly higher RSFC between the right FFA and right pSTS compared to the left pSTS [$M = -.14$ (-.24, -.03), $t(24) = -2.75$, $p = .01$], while the ASD group showed no difference between right and left pSTS connectivity with the right FFA [$M = .02$ (-.05, .09), $t(25) = .61$, $p = .54$]. This interaction was not observed for connectivity between the group-level bilateral pSTS and right FFA [$\chi^2(1) = 1.81$, $p = .18$] (Figure 5.6), nor was it observed for connectivity between the individually defined bilateral pSTS and right PPA control region [$\chi^2(1) = .17$, $p = .68$] (Figure 5.5). The group difference in integration scores was also significant [$t(47) = 1.85$, $p = .03$] (Figure 5.3), indicating that RSFC between the individually localized bilateral pSTS and FFA was right lateralized in the TD group ($M = -.14$) but not in the ASD group ($M = .07$).

The interaction between Group and Hemisphere also significantly improved model fit for connectivity between the individually defined right and left pSTS and left OFA [$\chi^2(1) = 5.53$, $p = .02$, $b = .13$, $SE_b = .05$] (Figure 5.3). Pairwise comparisons revealed that the ASD group showed significantly higher RSFC between the left OFA and left pSTS compared to the right pSTS [$M = .08$ (.004, .16), $t(25) = 2.16$, $p = .04$], while the TD group showed no difference between right and left pSTS connectivity with the left OFA [$M = -.05$ (-.13, .03), $t(24) = -1.2$, $p =$

.24]. The group difference in integration scores was also significant [$t(47) = 1.83$, $p = .03$] (Figure 5.3), indicating that RSFC between the individually localized bilateral pSTS and OFA was left lateralized in the ASD group ($M = .10$) and right lateralized in the TD group ($M = -.11$). A significant interaction between Group and Hemisphere was also observed for connectivity between the group-level bilateral pSTS and left OFA [$\chi^2(1) = 4.62$, $p = .03$, $b = .11$, $SE_b = .05$], and the group difference in integration scores was also significant [$t(47) = 1.83$, $p = .03$] (Figure 5.6), however these indicated that RSFC between the group defined bilateral pSTS and OFA was more strongly right lateralized in the TD group ($M = -.22$) than in the ASD group ($M = -.03$). This demonstrates that left lateralized RSFC between the pSTS and OFA in ASD participants is only evident with individual localization, and not in group defined ROIs.

The interaction between Group and Hemisphere was significant for connectivity between the individually localized bilateral OFA and both the right FFA [$\chi^2(1) = 5.88$, $p = .01$, $b = .13$, $SE_b = .05$] and the left FFA [$\chi^2(1) = 9.14$, $p = .002$, $b = .21$, $SE_b = .07$] (Figure 5.3). Pairwise comparisons revealed that the TD group showed stronger connectivity between the right FFA and right compared to the left OFA [$M = -.12$ (-.20, -.04), $t(24) = -3.21$, $p = .003$], while the ASD group showed no hemispheric difference in connectivity between the bilateral OFA and right FFA [$M = .009$ (-.07, .09), $t(25) = .25$, $p = .81$]. Pairwise comparisons further revealed that the ASD group showed stronger connectivity between the left FFA and left compared to the right OFA [$M = .15$ (.06, .25), $t(25) = 3.39$, $p = .002$], while the TD

group showed no hemispheric difference in connectivity between the bilateral OFA and left FFA [M = -.05 (-.15, .05), t(24) = -1.08, p = .29]. This interaction was not observed for connectivity between the individually localized bilateral OFA and the right PPA control region [χ^2(1) = .59, p = .44] or the left PPA control region [χ^2(1) = 2.47, p = .12] (Figure 5.5), nor was it observed for connectivity between the group-level bilateral OFA and the right FFA [χ^2(1) = .33, p = .56] (Figure 5.6). However, there was a marginal interaction in connectivity of the group-level bilateral OFA and the left FFA [χ^2(1) = 2.88, p = .09, b = .10, SE_b =.06]. The group difference in integration scores was also significant for individually localized ROIs [t(48) = 3.35, p < .001] (Figure 5.3), indicating that RSFC between the individually localized bilateral OFA and FFA was left lateralized in the ASD group (M = .16) and right lateralized in the TD group (M = -.17). The group difference in integration scores was marginally significant in the group-level bilateral OFA and FFA [t(48) = 1.43, p = .08] (Figure 5.6).

The interaction between Group and Hemisphere marginally improved model fit for connectivity between the individually localized bilateral BROC and left VWFA [χ^2(1) = 3.44, p = .06, b = -.10, SE_b =.05] (Figure 5.4). Pairwise comparisons revealed that the TD group showed significantly higher RSFC between the individually localized left VWFA and the left BROC compared to the right BROC [M = .16 (.08, .24), t(24) = 3.97, p < .001], while this hemispheric difference was only marginal in the ASD group [M = .06 (-.01, .13), t(25) = 1.74, p = .09]. The group difference in integration scores was significant [t(48) = -1.75, p = .04] (Figure

5.4), indicating that RSFC between the individually localized BROC and VWFA was more strongly left lateralized in the TD group (M = .22) than in the ASD group (M = .07). The interaction between Group and Hemisphere was not significant in the group-level bilateral BROC and left VWFA [$\chi^2(1) = .62$, $p = .43$], nor was the group difference in integration scores [$t(42) = -1.04$, $p = .15$] (Figure 5.6). The interaction between Group and Hemisphere was also not significant for connectivity between the individually localized bilateral BROC and the left LOC control region [$\chi^2(1) = .35$, $p = .55$], nor was there a group difference in integration scores [$t(48) = .11$, $p = .45$] (Figure 5.5).

There was a strong main effect of Hemisphere for connectivity between the individually localized bilateral WERN and left BROC [$\chi^2(1) = 20.91$, $p < .001$, $b = -.17$, $SE_b = .03$] (Figure 5.4), which was also evident in the group-level regions [$\chi^2(1) = 28.25$, $p < .001$, $b = -.16$, $SE_b = .03$] (Figure 5.6), indicating that RSFC between WERN and BROC is left lateralized across participants in both individually localized and group-level ROIs. There were no other hemispheric or group differences in the intrinsic functional connectivity of individually defined or group-level regions (ps > .10).

5.5 Discussion

The present work used resting-state fMRI to examine whether reduced functional specialization and/or reduced lateralization of critical regions involved in

language and face processing is an intrinsic property of functional network architecture in ASD. Data-driven multivariate analyses indicated decreased functional specialization of word processing regions (i.e., VWFA and pVWFA) in the ASD group, while hypothesis-driven univariate analyses indicated atypical hemispheric lateralization of RSFC between two critical regions for processing words (i.e., BROC and VWFA) as well as between all three core face network regions (i.e., pSTS, FFA, and OFA).

Multidimensional scaling and *k*-means clustering analyses of resting-state data across all 30 individually localized ROIs indicated decreased specialization of word processing regions in ASD (Figure 5.2). While the TD group demonstrated a separate cluster including the bilateral VWFA and pVWFA (i.e., word-related regions), the ASD group did not. Instead, the bilateral VWFA and pVWFA clustered with the bilateral FFA (i.e., critical for face processing) and PPA (i.e., critical for scene processing) in the ASD group. The other dissimilar cluster in the ASD group was made up of the more posterior category-related regions (i.e., bilateral OFA, OPA, and LOC, which are critical for processing faces, scenes, and nameable entities, respectively) and the bilateral pFS, which is also important for processing nameable entities. The elbow method demonstrated that four clusters best represented the data in each group separately, and the two clusters that did not comprise ventral visual regions were the same across groups (i.e., one comprised the bilateral AMG and ATL, and one comprised the bilateral pSTS, IFJ, BROC, WERN, and PCG). However, the category-related ventral visual areas clustered

differently between groups, whereby regions that process words and regions that process picture stimuli were clustered separately in the TD group, while clusters containing regions that process words and pictures were intermingled in the ASD group. This finding suggested reduced specialization of the functional network underlying word processing in ASD.

The lateralization of intrinsic functional connectivity between core regions for processing words and faces was further investigated in hypothesis-driven univariate analyses of the resting-state data. The hypothesized laterality difference (i.e., reduced leftward lateralization of RSFC between word processing regions in ASD) was observed between the individually localized BROC and VWFA (Figure 5.4). There was no group difference in the laterality of RSFC between BROC and LOC (i.e., a region important for processing nameable entities), demonstrating that reduced leftward lateralization of RSFC was specific to word processing regions (Figure 5.5).

The other hypothesized laterality difference (i.e., reduced rightward lateralization of RSFC between face processing regions in ASD) was observed between all three core face regions (Figure 5.3). That is, the TD group showed right lateralized RSFC between all the face processing regions, while the ASD group did not show right lateralized RSFC between any of them. Instead, the ASD group showed no hemispheric difference in connectivity between the pSTS and FFA, and furthermore, they showed left lateralized RSFC between the pSTS and OFA, as well as left lateralized RSFC between the OFA and FFA. There were no

group differences in the laterality of RSFC between face-related regions and the PPA (i.e., a region important for processing scenes), demonstrating that reduced rightward lateralization was specific to RSFC between face processing regions (Figure 5.5).

Despite existing neuroimaging literature that has established reduced leftward lateralization of the language network in ASD (Herringshaw et al., 2016; Joseph et al., 2014; Jouravlev et al., 2020; Kleinhans et al., 2008; Knaus et al., 2010; Lindell & Hudry, 2013), the present laterality differences were more evident in the face processing network. Group differences in the laterality of RSFC among face-related regions may have been stronger than that among word-related regions since the present sample included high functioning ASD participants with better language skills than those who are lower functioning. Indeed, the level of atypical leftward lateralization of the language system has been demonstrated to be related to the level of behavioural language impairment in ASD (Lindell & Hudry, 2013).

The present results further indicated the critical importance of individual localization of ROIs in each participant, especially when studying neurodiverse populations. There was no group difference in the laterality of RSFC between the group-level BROC and VWFA (Figure 5.6), hence individual localization was necessary to observe this result. While the lack of rightward lateralization of RSFC between face regions was also observed in the group-level regions, individual localization was necessary to observe the leftward lateralization of RSFC between

the OFA and the two other core face regions in the ASD group, further emphasizing the importance of individual localization of ROIs for fMRI analysis.

These results are an important contribution to the mixed literature on face processing in ASD. While converging evidence has established reduced leftward lateralization of language processing in ASD, individual localization was necessary to observe these effects in the face network. The present findings indicated that reduced rightward lateralization of face processing is concomitant with reduced leftward lateralization of language in ASD, and, as such, these phenomena may share similar underlying mechanisms.

Taken together, the present findings were aligned with the hypotheses that ASD participants would demonstrate reduced functional specialization of word-related regions (i.e., the multivariate results), as well as reduced left hemisphere lateralization of RSFC between word-related regions and reduced right hemisphere lateralization of RSFC between face-related regions (i.e., the univariate results). These findings indicated that reduced lateralization of language and face processing regions is an intrinsic property of functional network architecture in ASD, and not simply reflective of the use of different cognitive processing strategies during fMRI tasks.

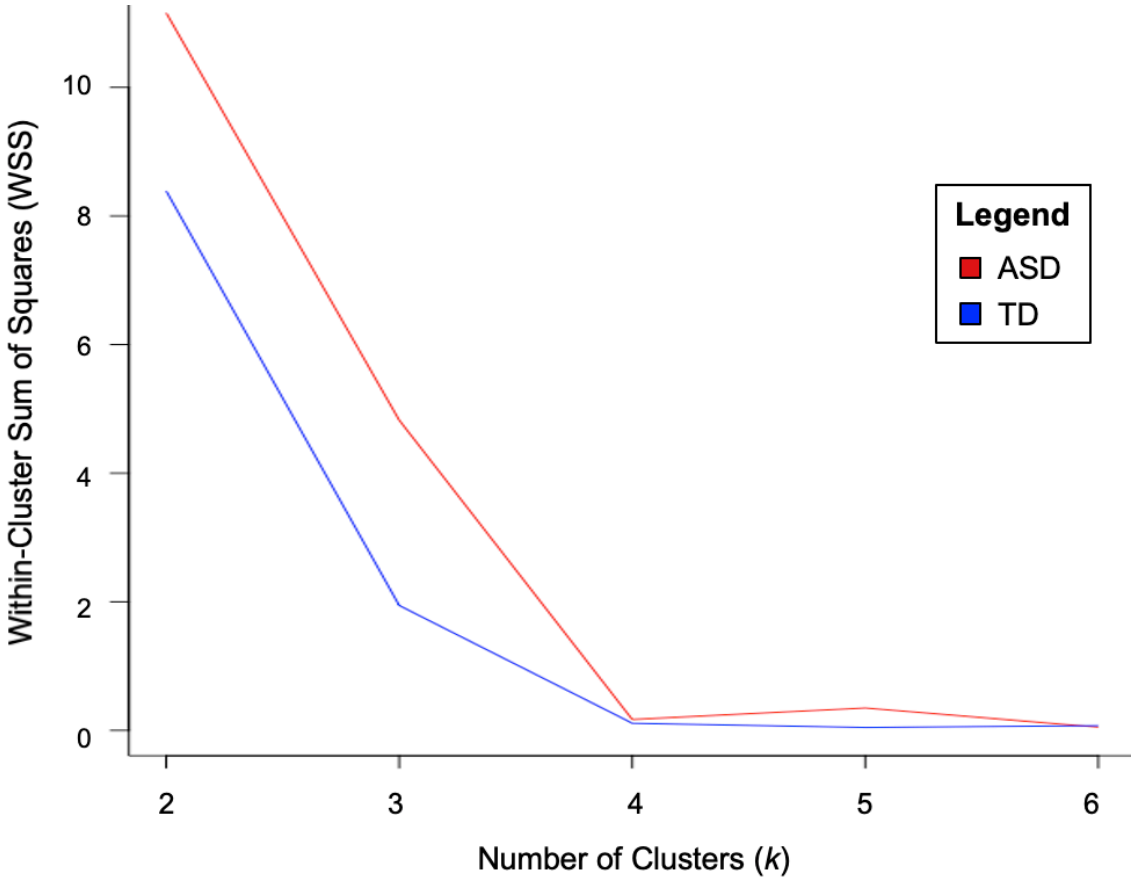

Figure 5.1. Elbow method to determine optimal number of clusters for *k*-means clustering. ASD = autism spectrum disorder; TD = typically developing; WSS = within-cluster sum of squares; *k* = number of clusters.

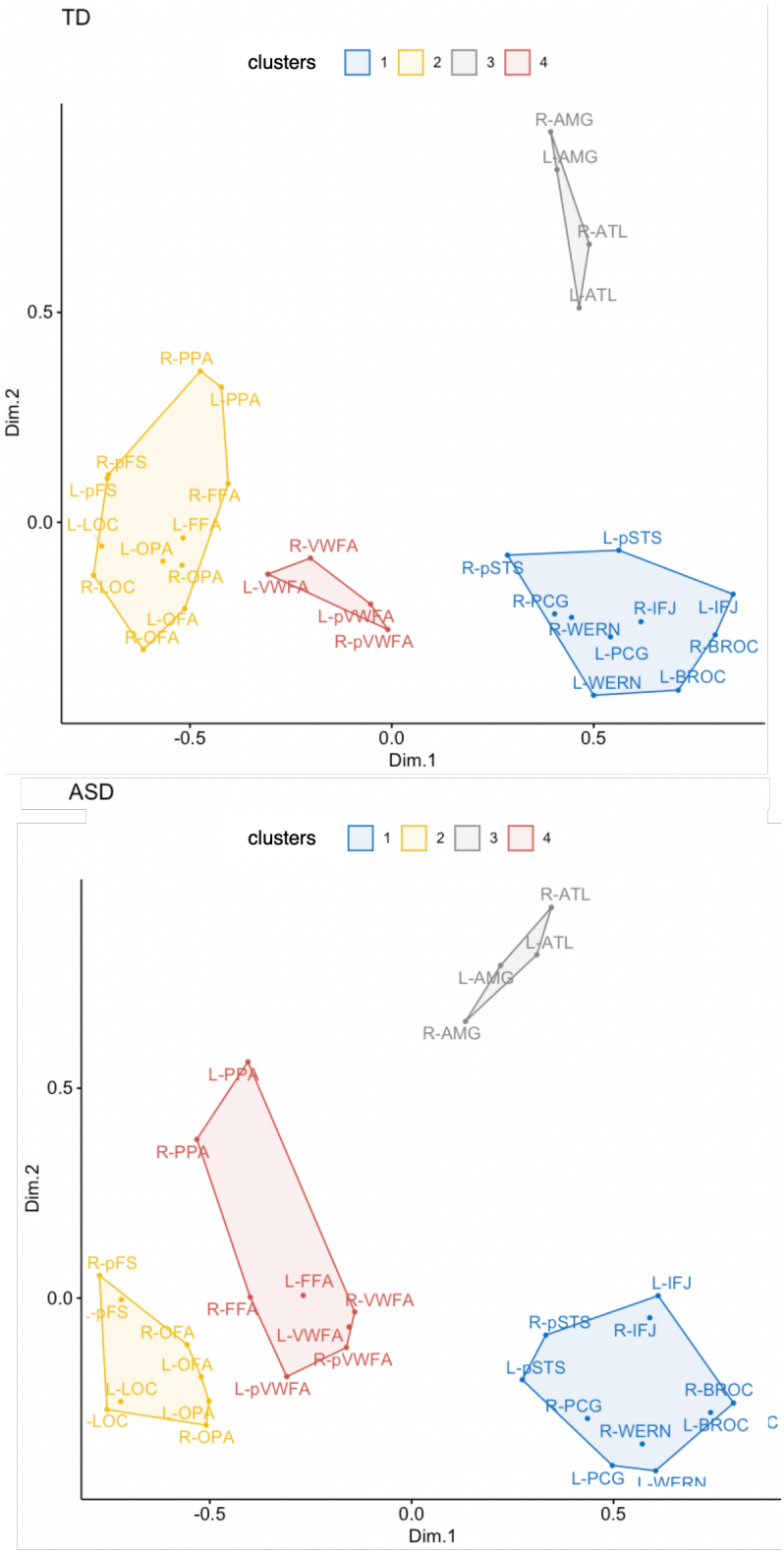

Figure 5.2. Multidimensional scaling and *k*-means clustering of intrinsic functional connectivity between individually localized regions in TD (top) and ASD (bottom) groups.

Multidimensional data are plotted in a common two-dimensional space such that similar objects are closer together. Dim = dimension (arbitrary units); ASD = autism spectrum disorder; TD = typically developing; L = left; R = right; *Face regions:* FFA = fusiform face area; OFA = occipital face area; pSTS = posterior superior temporal sulcus; IFJ = inferior frontal junction; ATL = anterior temporal lobe; AMG = amygdala; *Word regions:* VWFA = visual word form area; pVWFA = posterior VWFA; WERN = Wernicke's area; BROC = Broca's area; PCG = precentral gyrus; *Scene regions:* PPA = parahippocampal place area; OPA = occipital place area; *Nameable entity regions:* LOC = lateral occipital complex; pFS = posterior fusiform sulcus.

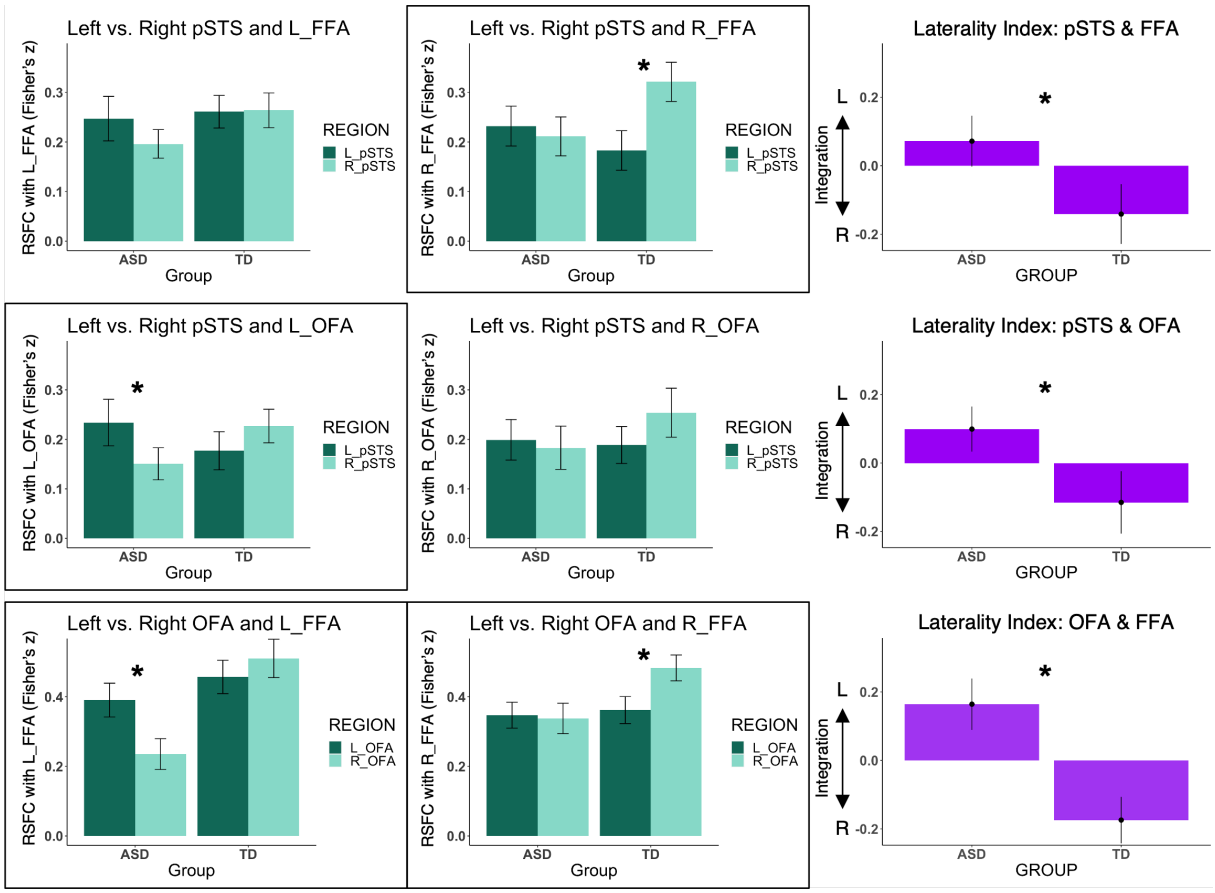

Figure 5.3. Laterality of intrinsic functional connectivity in individually defined core face regions. Panels with a significant Group x Hemisphere interaction are indicated with rectangular outlines. ASD = autism spectrum disorder; TD = typically developing; L = left; R = right; FFA = fusiform face area; OFA = occipital face area; pSTS = posterior superior temporal sulcus; * = $p < .05$.

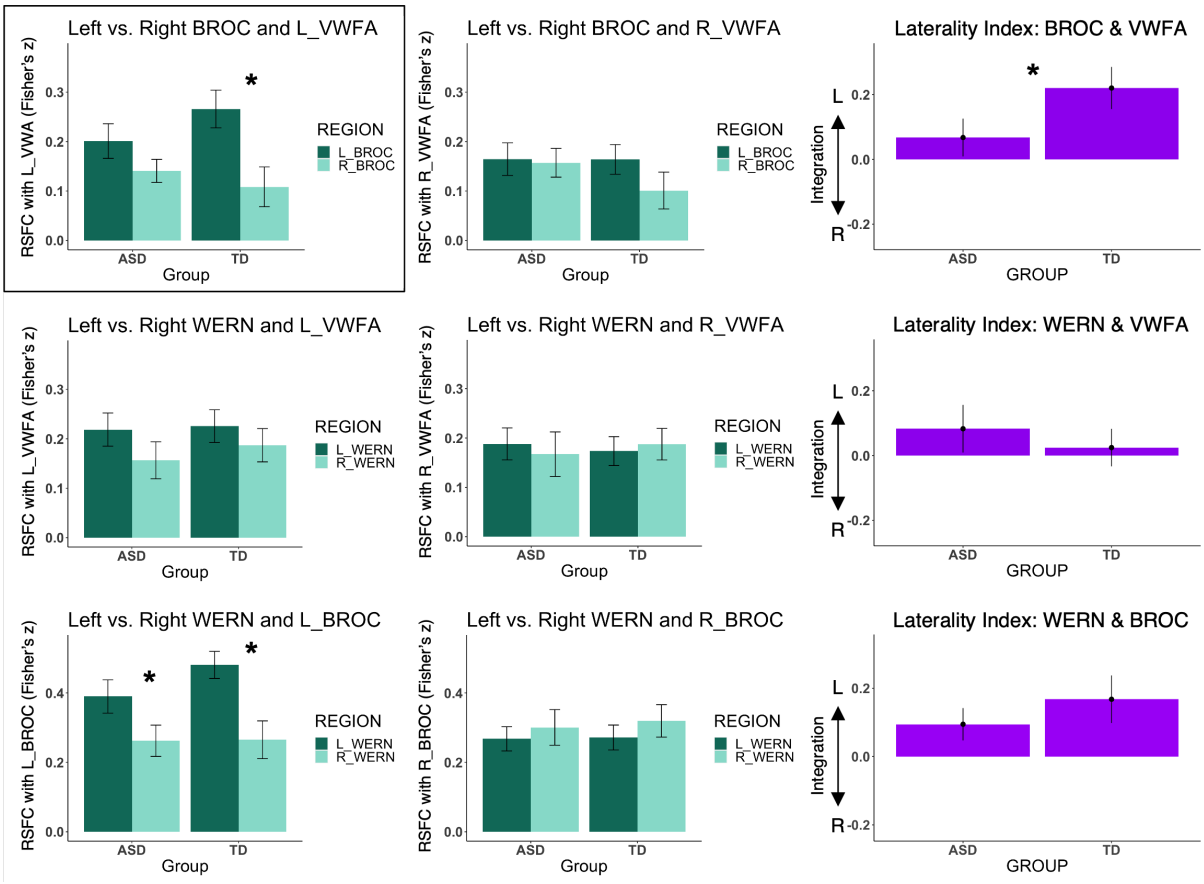

Figure 5.4. Laterality of intrinsic functional connectivity in individually defined core language areas. Panels with a significant Group x Hemisphere interaction are indicated with rectangular outlines. ASD = autism spectrum disorder; TD = typically developing; L = left; R = right; VWFA = visual word form area; WERN = Wernicke's area; BROC = Broca's area; * = $p < .05$.

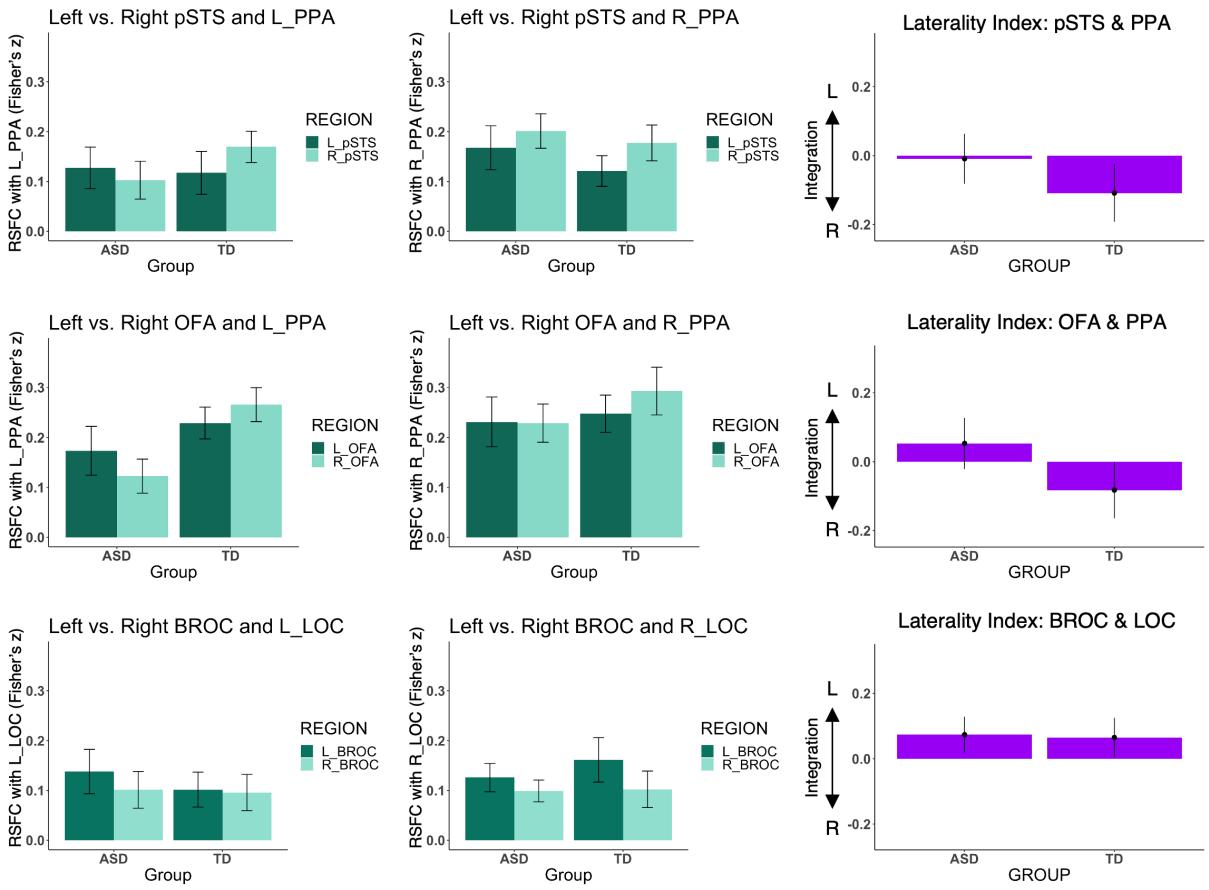

Figure 5.5. Control analyses for significant results in individually localized regions. ASD = autism spectrum disorder; TD = typically developing; L = left; R = right; OFA = occipital face area; pSTS = posterior superior temporal sulcus; PPA = parahippocampal place area; VWFA = visual word form area; BROC = Broca's area; LOC = lateral occipital complex.

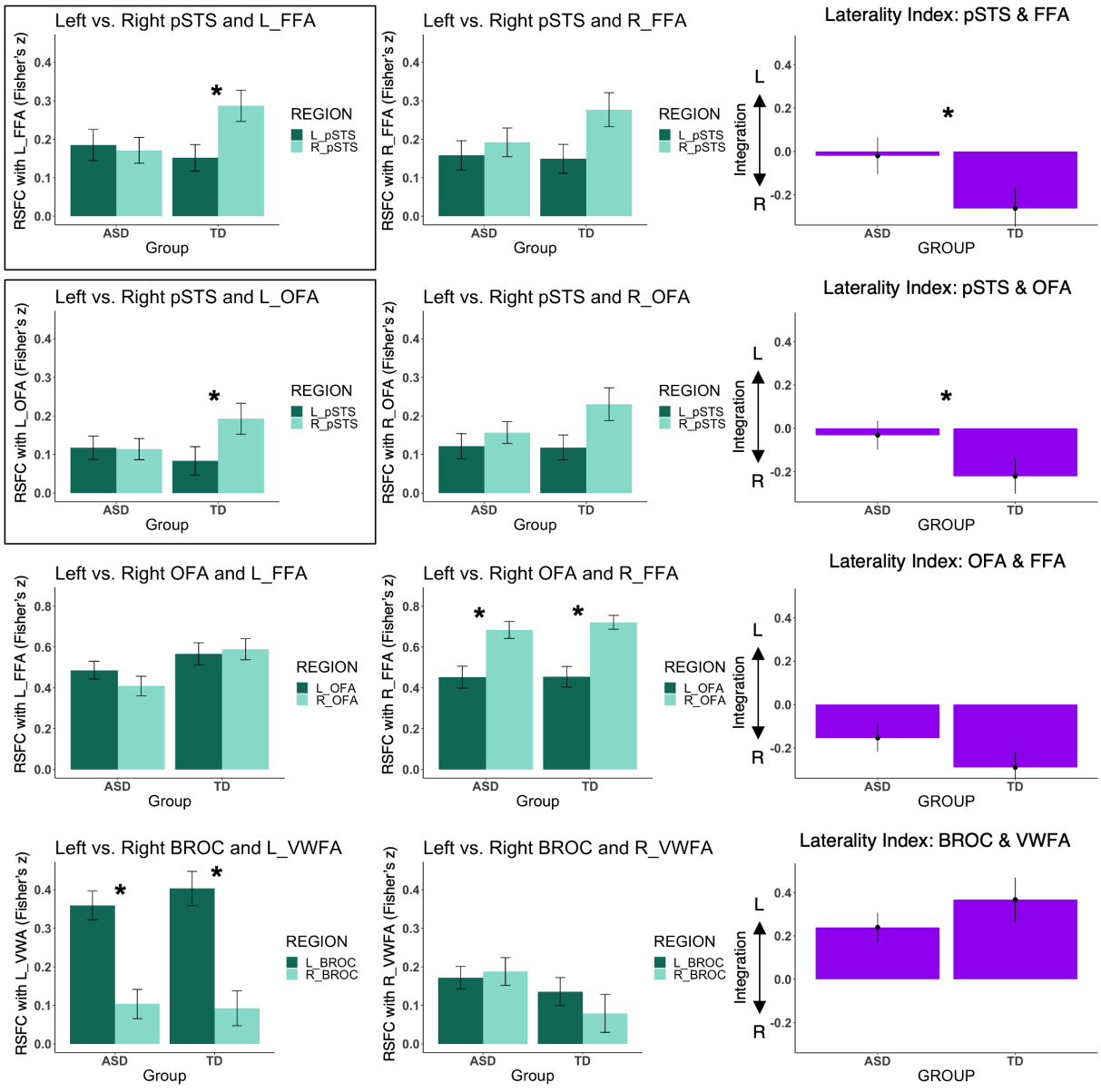

Figure 5.6. Laterality of intrinsic functional connectivity in group-defined face-related (top three rows) and word-related (bottom row) regions. Panels with a significant Group x Hemisphere interaction are indicated with rectangular outlines. * = $p < .05$; ASD = autism spectrum disorder; TD = typically developing; L = left; R = right; FFA = fusiform face area; OFA = occipital face area; pSTS = posterior superior temporal sulcus; VWFA = visual word form area; BROC = Broca's area.

CHAPTER 6:

General Discussion

6.1 Summary

The present dissertation aimed to explore the hemispheric lateralization of language and face processing in ASD. As hypothesized, autistic participants showed reduced functional specialization of language and face processing generally, and more specifically, reduced lateralization of both language in the left hemisphere and face processing in the right hemisphere, that was particularly evident in the pSTS. These findings were observed in analyses across all chapters, which included a quantitative fMRI meta-analysis, investigation of task-related fMRI activity, and investigation of intrinsic functional connectivity in resting-state fMRI data.

This investigation began with a quantitative fMRI meta-analysis in Chapter 2 in order to identify statistically reliable findings across multiple studies in the mixed existing literature, as well as to inform the rigorous study of matched groups of ASD and TD participants in the following chapters. Chapter 4 comprised a study of category-related brain activation in individually localized ROIs that are critical for language and face processing, while Chapter 5 investigated intrinsic functional connectivity between these ROIs.

The quantitative fMRI meta-analysis in Chapter 2 found that all clusters associated with language hyperactivation in ASD were situated in the right hemisphere, primarily in regions of the extended language network. Furthermore, the largest cluster showing hypoactivation for language was situated in the left inferior frontal gyrus extended back into the left lateral temporal cortex, i.e.,

classical language areas. Hypoactivation for language was also observed in the bilateral ACC, which has been implicated in neurotypical language processing, and in the left occipitotemporal sulcus, i.e., the purported location of the VWFA.

With respect to face processing, the meta-analysis found that the largest cluster that showed face-related hypoactivation in ASD was within the right fusiform gyrus, encompassing the location of the FFA. Another cluster that showed face-related hypoactivation in ASD was located within the right inferior occipital gyrus, encompassing the location of the OFA. The contrast analysis of within-group foci further revealed face-related hypoactivation in three right hemisphere regions that have typically been associated with face processing: the right amygdala and insula, right inferior occipital and middle temporal gyri, and right inferior frontal gyrus. Taken together, results from the meta-analysis indicated both reduced leftward lateralization of language and reduced rightward lateralization of face processing in ASD.

Striking evidence that ASD is related to atypical hemispheric asymmetry of both language and face processing came from the assessment of between-group overlap across cognitive domains in the meta-analysis. Overlaying the brain maps of between-group differences (i.e., ASD>TD and TD>ASD) separately for each cognitive domain (i.e., language and face processing) revealed clusters around the pSTS in both the left and right hemispheres that showed a crossover double dissociation between language and face processing in ASD relative to TD groups: 1) The left hemisphere region showed language-related hypoactivation and face-

related hyperactivation in ASD; 2) The right hemisphere region showed face-related hypoactivation and language-related hyperactivation in ASD. The pSTS was further implicated by the domain conjunction analysis of within-group contrasts, which examined whether any brain regions were reliably engaged in both language and face processing in either group. There were no areas associated with both language and face processing in TD groups. However, one cluster within the right pSTS was concordantly associated with both cognitive domains in ASD groups across studies. Thus, the meta-analysis in Chapter 2 demonstrated that reduced hemispheric specialization of language and face processing was especially evident in the pSTS (Figure 6.1).

The mean-centred PLS analysis of functional localizer data in Chapter 4 found that the TD group showed a significant LV separating covariance patterns for faces and words, while the ASD group did not, indicating reduced functional specialization in general for processing these categories in ASD. There was also no significant LV separating covariance patterns for faces and words when including both groups in the same analysis, further indicating reduced functional specialization in ASD.

Chapter 4 further examined category-related brain activation in individually localized ROIs (Figure 6.2). As suggested by results from the meta-analysis, reduced rightward lateralization was observed for face-related activation in the pSTS, where the TD group showed higher activation for faces in the right than left pSTS, while there was no hemispheric difference in the ASD group. While this

interaction was only significant for faces, word-related activation showed the expected pattern, where the TD group demonstrated higher activation for words in the left than right pSTS, while there was no hemispheric difference in the ASD group. The expected pattern was also observed for face-related activation in the group-level pSTS, but the overall amplitude of activation was much lower, indicating the importance of individual localization.

The hypothesized reduction in leftward lateralization of word-related activation was observed in the individually localized VWFA, where the TD group showed higher activation for words in the left than right VWFA, while the ASD group showed no hemispheric difference. This effect was specific to words, as it was not observed for face-related activation. This effect was also not observed in the group-level VWFA, demonstrating the importance of individual localization. Interestingly, the level of rightward lateralization of face-related activation in the pSTS and the level of leftward lateralization of word-related activation in the VWFA were correlated in the ASD group, but not in the TD group, suggesting that there could be a common underlying cause of reduced lateralization in these regions in ASD.

The multidimensional scaling and *k*-means clustering analysis of intrinsic functional connectivity in Chapter 5 revealed reduced functional specialization of RSFC between regions that are critical for word processing. That is, the VWFA and pVWFA clustered together separately from other ROIs in the TD group. However, the VWFA and pVWFA clustered with the FFA and PPA in the ASD

group, which are critical regions for processing faces and scenes, respectively. Hence, this analysis demonstrated reduced functional specialization of RSFC between regions that process words and pictures in the ASD group.

Chapter 5 further examined intrinsic functional connectivity between individually localized ROIs in targeted laterality analyses (Figure 6.2). Reduced leftward lateralization of RSFC was observed between the VWFA and Broca's area, while reduced rightward lateralization of RSFC was observed between all three core face regions (i.e., pSTS, FFA, and OFA). Furthermore, individual localization was necessary to observe these effects.

While previous work has demonstrated that autistic individuals tend to show reduced left hemisphere lateralization of language that is correlated with the level of behavioural impairment in this domain (Lindell & Hudry, 2013), differences in the lateralization of RSFC in the present sample were more evident among face regions. This could be because ASD participants in this sample were high functioning with better language skills than those included in other studies.

This work is an important contribution to the mixed literature on face processing in ASD since it uses more rigorous and comprehensive techniques to resolve previous inconsistencies. The existing neuroimaging literature on face processing in autism is mixed, likely due to discrepancies in how ROIs are identified for fMRI analyses. The results from Chapter 4 and Chapter 5 add to a growing body of literature demonstrating the importance of individual ROI localization to account for individual differences (e.g., Glezer & Riesenhuber, 2013;

Stevens et al., 2017) since the main findings were not observed in ROIs defined at the group level. This may be especially important in neurodiverse populations.

6.2 Limitations

Relatively small and homogeneous groups were examined in Chapter 4 and Chapter 5 (i.e., 26 ASD males and 25 TD males, matched on average age, IQ, and head motion parameters). The meta-analysis in Chapter 2 also comprised disproportionately more male than female participants. This is a consequence of most ASD research being conducted on males (Cascio et al., 2021). In Chapter 2, only 84/1036 ASD participants and 111/1090 TD participants were female in total, i.e., fewer than 10% of participants included in the meta-analysis were female. Therefore, the present results are not generalizable to female autistic individuals. Interactions between sex and ASD diagnosis have been demonstrated in brain regions that show sex differences in neurotypical groups (Walsh et al., 2021).

The meta-analysis included both visual and auditory language studies to increase statistical power, while all the face processing studies were visual. Furthermore, most of the stimuli in the face processing studies included in the meta-analysis, as well as the stimuli presented here in Chapter 3, comprised static images of faces. However, previous work has demonstrated that posterior lateral temporal cortex is more strongly driven by dynamic rather than static images of faces (Bernstein & Yovel, 2015).

6.3 Future Directions

Future work should use individual localization of ROIs with larger and more varied samples of participants. Research with female autistic participants is especially crucial, since most existing studies have been conducted with males.

Future work should also use dynamic rather than static face stimuli, and it should further investigate the relationship between different components of language and face processing in ASD, such as identity or emotion discrimination.

The present results suggest the pSTS would be a good candidate for experimental investigation using noninvasive brain stimulation (NIBS). While a small number of previous NIBS studies of ASD have applied stimulation to the pSTS, most of them have focused on the dorsolateral prefrontal cortex (Khaleghi et al., 2020).

The fMRI dataset presented here could be further examined using a technique called representational similarity analysis (RSA; Kriegeskorte, 2008). RSA is a method of quantitatively relating different measures of neural activity, such as RSFC and category-related brain activation (e.g., Chen et al., 2017), by abstracting from the activity patterns themselves and computing representational dissimilarity matrices (RDMs) that characterize the information contained in the measured brain signal (Kriegeskorte, 2008). RSA would be a useful technique to elucidate the relative roles of the left and right pSTS in language and face processing in ASD.

6.4 Conclusion

The pSTS is a critical brain region for processing dynamic faces, multisensory integration, biological motion, and theory of mind, which are all cognitive functions that can be impacted in ASD (Frith, 2001; Koldewyn et al., 2011; Yang et al., 2015). A third visual pathway for social perception on the lateral brain surface has been proposed, beyond the classical “what” and “how” ventral and dorsal pathways, respectively (Pitcher & Ungerleider, 2021). This model posits that information is sent from early visual cortex to the pSTS via motion-selective areas to be integrated with information from other sensory modalities in order to support the ability to understand and interpret the actions of others. Atypical hemispheric specialization of the posterior lateral temporal cortex could play an integral role underlying the social/communication difficulties experienced in autism.

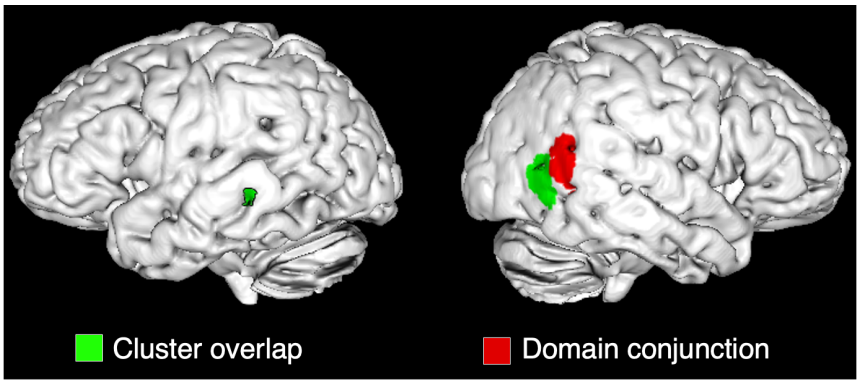

Figure 6.1. Quantitative fMRI meta-analysis: Cluster overlap of between-group foci across domains shown in green (i.e., a left hemisphere region related to language processing in TD groups and face processing in ASD groups, and a right hemisphere region related to face processing in TD groups and language processing in ASD groups), and domain conjunction of within-group foci shown in red (i.e., a right hemisphere region related to both domains in the ASD group).

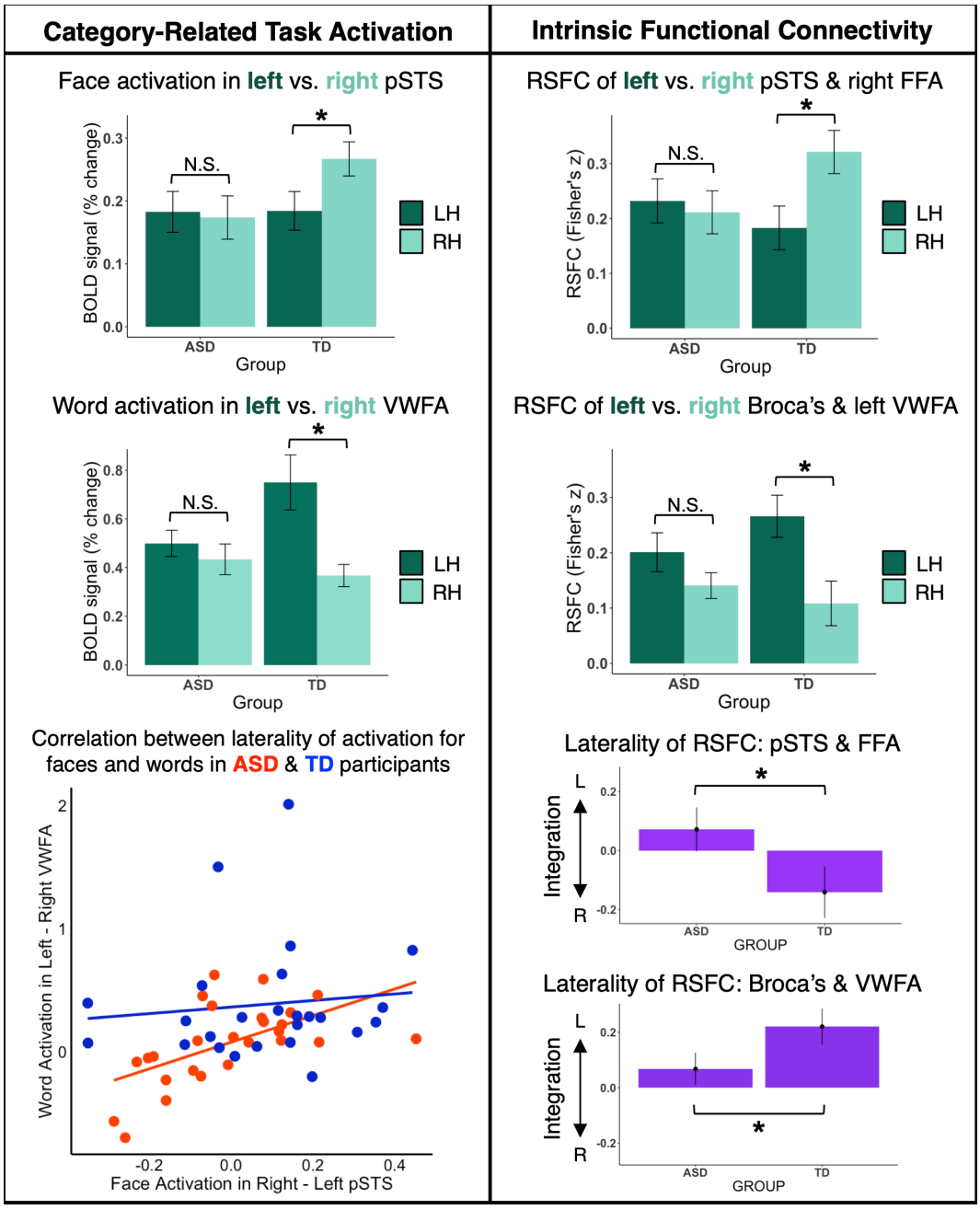

Figure 6.2. Hemispheric lateralization of category-related brain activation (left) and intrinsic functional connectivity (right) in the bilateral posterior superior temporal sulcus (pSTS) and visual word form area (VWFA). ASD = autism spectrum disorder; TD = typically developing; LH = left hemisphere; RH = right hemisphere; L = left; R = right; FFA = fusiform face area; N.S. = not significant; * = $p < .05$.

Pearson correlation between lateralization of VWFA for words and pSTS for faces was significant in the ASD ($r = .57$, $p = .002$) but not TD ($r = .11$, $p = .61$) group.

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Appendix A: Mean-Centred PLS Results in ASD Group

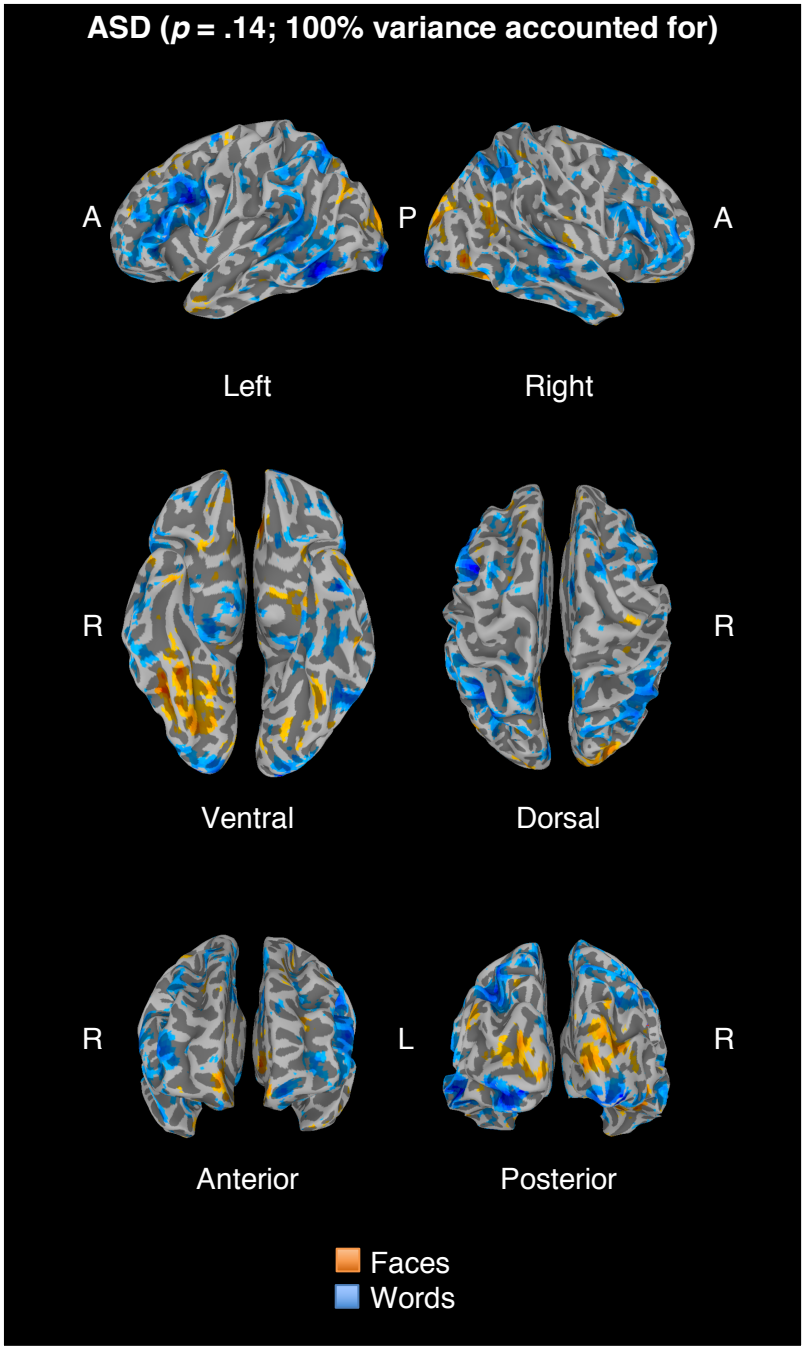

Figure A.1. Spatiotemporal patterns of brain activation in response to faces (warm colours) and words (cool colours) from mean-centred partial least squares (PLS). ASD = autism spectrum disorder; A = anterior; P = posterior; L = left; R = right.

Appendix B: Group-Level Results in ROIs Defined by Meta-Analysis

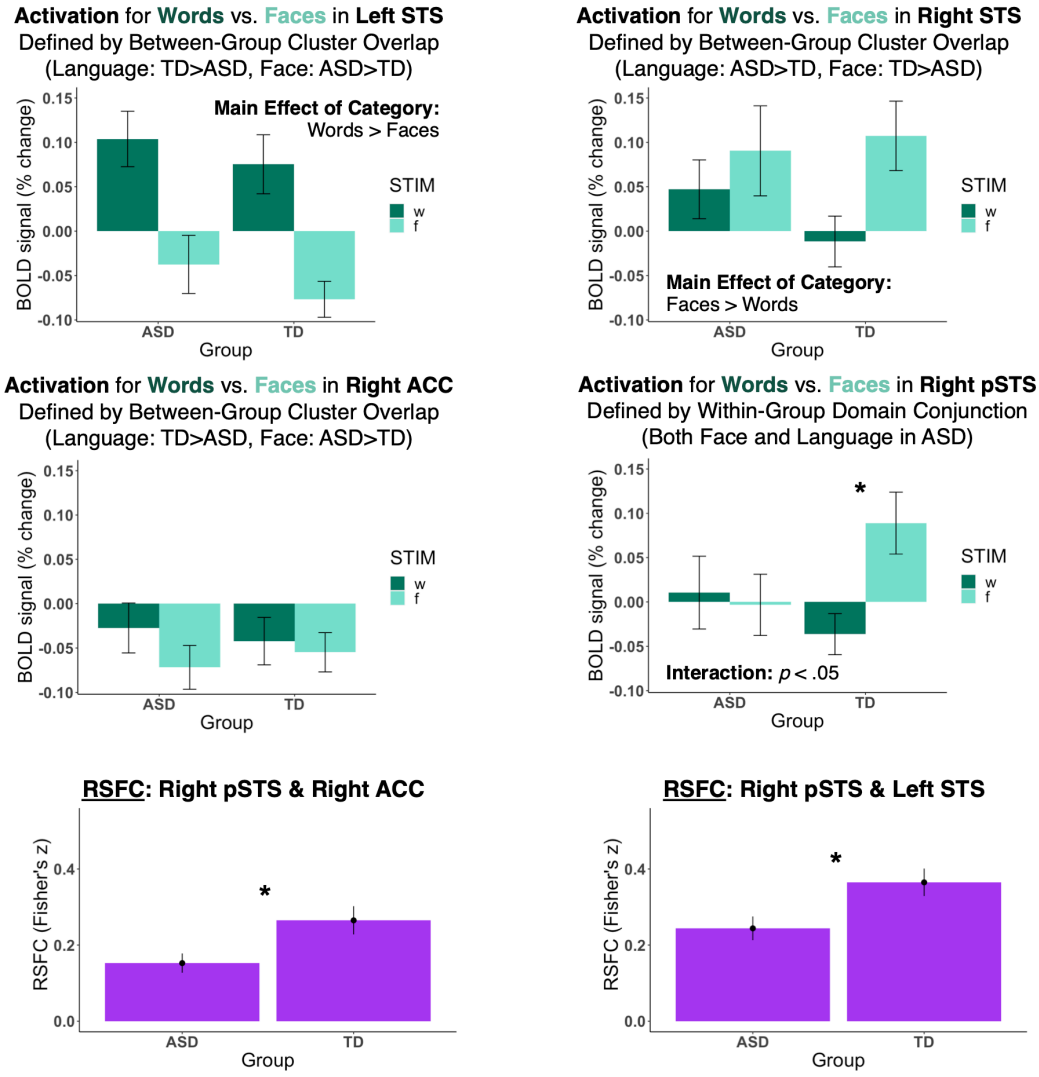

Figure B.1. Group-level task and rest results in regions of interest (ROIs) defined by meta-analysis. Domain = language or face processing; between-group overlap = clusters related to one domain in one group and the other domain in the other group; within-group domain conjunction = clusters related to both domains in one group; ASD = autism spectrum disorder; TD = typically developing; STS = superior temporal sulcus; pSTS = posterior STS; ACC = anterior cingulate cortex; * = $p < .05$; STIM = stimulus category; f = face; w = word.