Atypicalities in cortical structure, handedness, and functional lateralization for language in autism spectrum disorders.

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Word Count: 11,208

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Language is typically a highly lateralized function, with atypically reduced or reversed lateralization linked to language impairments. Given the diagnostic and prognostic role of impaired language for autism spectrum disorders (ASDs), this paper reviews the growing body of literature that examines patterns of lateralization in individuals with ASDs. Including research from structural and functional imaging paradigms, and behavioral evidence from investigations of handedness, the review confirms that atypical lateralization is common in people with ASDs. The evidence indicates reduced structural asymmetry in fronto-temporal language regions, attenuated functional activation in response to language and pre-linguistic stimuli, and more ambiguous (mixed) hand preferences, in individuals with ASDs. Critically, the evidence emphasizes an intimate relationship between atypical lateralization and language impairment, with more atypical asymmetries linked to more substantive language impairment. Such evidence highlights opportunities for the identification of structural and functional biomarkers of ASDs, affording the potential for earlier diagnosis and intervention implementation.

**Keywords:** language; autism spectrum disorders; brain; asymmetry; hemisphere; review
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Autism spectrum disorders (ASDs) are a cluster of conditions affecting at least 1% of the population (see Barbaro & Dissanayake, 2010; Baird, Simonoff, Pickles, Chandler, Loucas, et al., 2006; Centers for Disease Control and Prevention [CDC] 2012). According to current diagnostic systems, ASDs are classified as Pervasive Developmental Disorders, including specific conditions such as Autistic Disorder, Asperger syndrome, and Pervasive Developmental Disorder – Not Otherwise Specified (PDD-NOS; American Psychiatric Association [APA], 2000; World Health Organisation, 1992). Common among these is a symptom triad comprising impairments in skills for social interaction and communication, alongside restricted/stereotyped patterns of interest and behaviour.

Beyond these diagnostic commonalities, however, significant heterogeneity presents among diagnosed individuals, in terms of specific symptom presentation, the severity thereof, and many other features of individual functioning, including cognitive ability (see Waterhouse, 2013, for very comprehensive recent consideration of this topic, and Boucher, 2012, for a review specifically regarding language). While the reasons for and mechanisms by which ASD symptoms come to present in affected individuals remain to be clearly demonstrated, it is becoming increasingly apparent that multiple causal processes must be at play, given the significant heterogeneity that pervades ASDs (see Waterhouse, 2013). Most easily observable and accepted is the variability that presents in overt behavioural symptoms as well as in the presenting cognitive phenotype. While some individuals with ASDs experience significant symptom expression alongside profound cognitive and functional impairment (often referred to as low-functioning individuals), many present average or above-average intelligence (commonly referred to as high-functioning individuals) and may have relatively subtle social-communication difficulties. A characteristic cognitive/developmental profile presenting commonly among individuals
with ASDs comprises relative sparing of visuo-spatial skills, impairments in motor skills (for both gross coordination and fine control; see Bhat, Landa, & Galloway, 2011), and greatest impairments in the domain of language (e.g., Hudry, Leadbitter, Temple, Slonims, McConachie, et al., 2010).

Although ASDs are considered to be neurodevelopmental in nature (e.g., see Elsabbagh, Mercure, Hudry, Chandler, Pasco, et al., 2012), relatively little is known about the neural underpinnings of overt behavioral symptoms. Diagnosis, reliant on the examination of an individual’s behavioural presentation, is usually established in toddlerhood or early childhood but may be significantly delayed beyond this point where subtle symptoms present alongside spared language (e.g., Mandell, Novak & Zubritsky, 2005). Nevertheless, the developmental pathway toward ASD-outcome is likely to have its onset very early in life, well before concerns are raised and diagnosis is sought (Elsabbagh & Johnson, 2010). Multi-faceted heterogeneity, relatively late diagnostic identification, and the truly developmental nature of ASDs contribute together to the challenge inherent in understanding this cluster of conditions drawn together by a common symptom set and characteristic cognitive phenotypic profile.

"Language is central to both diagnosis and prognosis in autism", (Herbert, Harris, Adrien, Ziegler, Makris, et al., 2002, p.588). Whilst the presence of speech before age five is typically cited as the strongest predictor of more favourable outcomes (e.g., Mody & Belliveau, 2012), recent research suggests that the production of a child's first words by age two may be an even stronger predictor of better outcomes (Mayo, Chlebowski, Fein, & Eigsti, 2013). However, while impairments in communication are core to the diagnosis of all ASDs, language delays present only in the case of Autistic Disorder and not where the diagnosis is Asperger syndrome (Howlin, 2003). Where present, language impairments manifest variously, and neuropsychological investigation is vital to further our
understanding, illuminating the relationship between aberrations in cortical structure and atypical behavioral function, and affording an opportunity to elucidate phenotypic variation in ASDs (Stefanatos & Baron, 2011).

In terms of cortical representation, language has long been argued to be a predominantly left hemisphere function, prompted by the observed coincidence of left hemisphere damage and articulate language deficits (Broca, 1865). However, while the left hemisphere is clearly the superior language processor, the right hemisphere is also vital for efficient language processing as it controls aspects including prosody and pragmatics (see Lindell, 2006, for review). Given that reduced or reversed patterns of lateralization are associated with language impairments (e.g., de Guibert, Maumet, Jannin, Ferré, Tréguier, et al., 2011), and that language impairments are often present in ASDs, examination of the patterns of hemispheric asymmetry in people with ASDs is needed to help establish the relationship between atypicalities in cortical lateralization and the behavioral manifestations of the disorder.

Consequently, this review seeks to shed light on the nature of hemispheric asymmetry in individuals with ASDs by examining atypicalities in structural brain lateralization, observed handedness, and functional lateralization. Further, it aims to examine the relationships between atypical lateral asymmetries (structural, manual, and functional) in individuals with ASDs and behavioral symptoms such as language impairment, culminating in a model that describes the proposed relationships between atypical asymmetries and the behavioral characteristics of ASDs. In doing so, the review will characterise the current knowledge base of ASD laterality research, paving the way toward directions for future investigation.

*Structural Lateralization*
According to Tager-Flusberg and Caronna (2007), most, but not all, children with ASDs have receptive and expressive language impairments. Thus, given that disordered language presents commonly in ASDs, and given also that language is considered the paradigmatic lateralized function, one might predict that people with ASDs would exhibit atypical patterns of cortical lateralization. Indeed, it has even been suggested that ASDs reflect left hemisphere brain damage (e.g., McCann, 1981). However, despite the bold claim that "autism is referred to as cerebral lateralization abnormality," (Dane & Balci, 2007, p.223), it is not clear that such a definitive stance has yet been adopted by the academic or clinical communities. Although attempts to define the neuroanatomy of ASDs are still in their infancy (Amaral, Schumann, & Norsahl, 2008), recent years have seen a marked increase in research seeking to understand its neural foundations (Stafanatos & Baron, 2011); even so, "hemisphere laterality is an area which remains relatively unexplored in autism," (Ecker, Marquand, Mourão-Miranda, Johnston, Daly, et al., 2010, p.10621). This is perhaps surprising, especially given that atypical cerebral asymmetry is considered a risk factor for a number of neurobehavioral disorders (Moncrieff, 2010; Smalley, Loo, Yang, & Cantour, 2004). Accordingly, here we examine research investigating structural asymmetries in people with ASDs to evaluate the evidence of atypical patterns of hemispheric lateralization.

Research investigating cortical structure has typically used magnetic resonance imaging (MRI) to shed light on cerebral architecture. Data from studies using such techniques implicate left hemisphere abnormality in people with ASDs. For example, Ecker et al. (2010) used a support vector machine (SVM) analytic approach to assess cortical anatomy in adults with ASDs. Their SVM data indicate that the left hemisphere is more "abnormal" in adults with ASDs than the right hemisphere, allowing the authors to accurately classify 79% of adults with ASDs from the left hemisphere, versus 65%
classification accuracy from the right hemisphere. As SVM is a relatively new technique, it remains to be determined whether similar patterns of abnormality (and accompanying classification/prognosis accuracy) are present earlier on the development course toward ASDs.

Focusing specifically on structural asymmetries in language association areas of the cortex, Herbert et al. (2002) reported that children with ASDs (7 – 11 years) exhibit a reversal of the typical leftward asymmetry. Whereas typically-developing controls had 17% greater matter in the left inferior lateral frontal and posterior superior temporal regions (coincident with Broca’s and Wernicke’s areas respectively), boys with ASDs exhibited reversed asymmetry in these regions, with 27% greater matter in the right hemisphere. Given the crucial role that these cortical areas play in language processing and production, greater relative size of left hemisphere volumes in the frontal and temporal regions are not only typical, but index greater language ability (e.g., Morgan & Hynd, 1998). Thus, the fact that children with ASDs show reversed asymmetry in these regions, with greater volume in the right hemisphere, evidences atypical cortical organisation, suggesting that this atypicality may play a causal role in the language disturbance evident in ASDs.

Further evidence of atypical cortical organization in ASDs is offered by Gage, Juranek, Filipek, Osann, Flodman, et al. (2009) who reported rightward asymmetry in the auditory association areas (posterior superior temporal gyrus and planum temporale) of children with ASDs (2 – 14 years). The pattern of leftward asymmetry for Heschl’s gyrus (a region of the superior temporal gyrus housing the primary auditory cortex) was similar to that observed in the controls, suggesting that the developmental trajectory of gray matter in this region is consistent with that observed in the typically-developing population. Both De Fossé, Hodge, Makris, Kennedy, Caviness Jr., et al. (2004), and
Bigler, Mortensen, Neeley, Ozonoff, Krasny, et al. (2007) similarly found no difference in gross morphology and volume of the superior temporal gyrus between children with ASDs and typically-developing controls. This consistency may be limited to gray matter, as research by Lange, DuBray, Lee, Froimowitz, Froelich, et al. (2010) indicates reversal of the typical leftward white matter asymmetry in diffusion tensor skewness in the superior temporal gyrus in people with ASDs. This reversal denotes that directional diffusion, and thus communication, is more coherent in the right superior temporal gyrus in people with ASDs, suggesting anomalous lateralization of white matter microstructure in this critical language region.

For the planum temporale, Gage et al.’s (2009) research indicates that the maturational pathway differs: whereas typically-developing children exhibit a leftward volumetric bias, children with ASDs show a rightward asymmetry that increases with age. As Gage et al.’s data are cross-sectional rather than longitudinal, further research is needed to confirm this difference in planum temporale development, particularly as data from other investigators indicate reduced, rather than reversed, planum temporale asymmetry in both children (5 – 16) and adults with ASDs (Rojas, Camou, Rete, & Rogers, 2005; Rojas, Bawn, Benkers, Reite, & Rogers, 2002), and reduced leftward asymmetry in the long-range fibre tracts (cingulum, arcuate fasciculus, uncinate fasciculus) connecting the frontal and temporal lobes in adolescents (14 – 17 years) with ASDs (Lo, Soong, Gau, Wu, Lai, et al., 2011).

Assessment of regional cerebral blood flow also offers evidence of abnormal asymmetry, with children with ASDs (4 – 17 years) showing greater blood flow in the right than left hemisphere, whereas typically-developing controls exhibit the opposite pattern (Chiron, Leboyer, Leon, Jambaque, Nuttin, & Syrota, 1998; see also Hashimoto, Sasaki, Fukumizu, Hanaoka, Sugai, & Matsuda, 2000). This reversed asymmetry reflects reduced blood flow in children with ASDs across the left hemisphere, including language-
related cortex. Such findings appear consistent with microscopic investigations indicating accelerated neuronal death in Wernicke's area (Brodmann 22) in children with ASDs after age seven (López-Hurtado & Prieto, 2008).

Herbert, Ziegler, Deutsch, O'Brien, Kennedy, et al. (2005) used a nested, whole-brain MRI analysis to examine cortical asymmetries at both large and smaller units of analysis. The results of their comparison of boys with ASDs (7 – 11 years), boys with developmental language disorder (characterized by language impairment in the absence of social impairment), and typically-developing controls, indicated that patterns of cortical asymmetry in the boys with ASDs and developmental language disorder were more similar to one another than either group was to the controls. In particular, data indicated no asymmetries at the hemispheric, lobular, or major grey/white matter structure level of analysis for boys with ASDs and developmental language disorder, whereas controls demonstrated asymmetries in these regions. Analysis of more fine-grained parcellation units indicates that whereas control participants exhibit an overall left hemisphere-biased volumetric asymmetry, this bias is reversed in boys with ASDs and boys with developmental language disorder who both exhibit rightward structural asymmetries (see also Hier, LeMay, & Rosenberger, 1979). This reversal in anatomical asymmetry was widely distributed, suggesting that the neural system disruption involved in ASDs (and developmental language disorder) is pervasive, rather than localized to specific function circuits.

De Fossé et al.'s (2004) data appear consistent, confirming reversal of asymmetry in language association cortex in language-impaired boys (6-13 years) with ASDs. Critically, De Fossé et al.'s investigation demonstrated a clear link between language disturbance and reversed asymmetry: whereas language-impaired boys with ASDs exhibited a right-biased frontal cortex asymmetry, boys with ASDs but without concomitant language impairment
showed a left-biased frontal asymmetry indistinguishable from typically-developing controls. The fact that a comparison group of boys with specific language impairment (SLI, also known as developmental language disorder) also showed a right-biased frontal asymmetry suggests that reversed asymmetry may be related to language impairment, rather than ASDs per se, a suggestion echoed by Knaus et al. (2010). The findings of reversed inferior frontal cortex asymmetry in language-impaired boys with ASDs and boys with SLI has since been replicated (Hodge, Makris, Kennedy, Caviness Jr, Howard, et al., 2010).

The relationship between reduced left frontal volume and language ability in ASDs was further consolidated by McAlonan, Suckling, Wong, Cheung, Lienenkaemper, et al. (2008). They examined gray matter volume in children (7 – 16 years) with high-functioning autism, Asperger syndrome, and typically-developing controls, finding reduced left hemisphere frontal volumes in the children with high-functioning autism in comparison with the controls. Moreover, there was a significant negative correlation, of moderate effect size, between gray matter volume in the left inferior frontal gyrus (Brodmann's area 44) and delayed age of acquisition of phrase speech in children with high-functioning autism, implying a relationship between reduced cortical volume in Brodmann's language area and language delay. Importantly, this correlation was restricted to the children with both ASDs and language impairment (i.e., the subgroup with high-functioning autism) and was not evident in those with specific diagnoses of Asperger syndrome, again suggesting that atypical lateralization is a characteristic of language impairment more generally, rather than ASDs specifically.

This distinction is important and it may help explain why Brieber, Neufang, Bruning, Kamp-Becker, Remschmidt, et al. (2007) reported no frontal volume differences between adolescents with ASDs (10 – 16 years) and controls (there was, however, reduced left
medial temporal volume in the ASD group). The ASD sample tested by Brieber et al. (2007) comprised 13 children with Asperger syndrome and two children with high-functioning autism. Given that substantive delay in language acquisition is, by definition, not present in the former subgroup, and that McAlonon et al.’s (2008) data indicate that atypical frontal asymmetries are linked to delayed language acquisition, the fact that 87% of Brieber et al.’s (2007) ASD sample had a diagnosis of Asperger syndrome and hence, no language delay, may help explain the absence of reduced inferior frontal asymmetry.

Although a number of investigations have offered evidence of reduced or reversed cerebral asymmetry in people with ASDs, not all studies have found atypical patterns of lateralization. For example, Hazlett, Poe, Gerig, Smith, Provenzale, et al.’s (2005) examination of brain size and structure in infants and toddlers with ASDs (birth – 2 years) indicated brain enlargement in comparison with both typically-developing and developmentally-delayed control groups. However, none of the groups of children showed evidence of structural asymmetry at this age, implying that the previously-noted volumetric differences are likely to emerge developmentally, and in response to the environment, rather than being present at birth. That said, Rumsey, Creasey, Stepanek, Dorward, Patronas, et al.’s (1988) computerized transverse axial tomography (CT) study indicated no differences in patterns of hemispheric width between men with ASDs (18 – 39 years) and controls. However, as individuals within this small sample (N = 15) varied substantially in the level of cognitive ability presenting alongside their ASD diagnosis (i.e., three individuals had language-specific cognitive impairments while another three presented global cognitive impairments), and given that this measurement technique lacks the precision of current voxel-based MRI methods, inferences from these data should be drawn with caution.
A more recent investigation found an increased, rather than reduced or reversed, asymmetry in left hemisphere gray matter volume in adolescent and adult males with ASDs (13 – 29 years; Hazlett, Poe, Gerig, Smith, & Piven, 2006). Importantly, this increase was restricted to the frontal and temporal lobes (i.e., increased volume in the language association areas for which De Fossé et al. (2004) and Herbert et al. (2005) found a rightward volumetric enlargement). Given that typically-developing controls usually exhibit greater left than right hemisphere volumes in these regions, the fact that adolescent and adult males with ASDs show an exaggerated leftward bias again offers evidence of cortical atypicality in ASDs, though admittedly in a different pattern to the majority of the literature.

Research examining brain structure in people with ASDs clearly indicates that atypical patterns of cortical asymmetry are characteristic of the disorder. That said, the inconsistencies in findings may be at least partially attributed to the variability in ages of the populations tested and the, perhaps necessarily, small sample sizes (Siegal & Blades, 2003); in addition, one of the challenges of generalising from such research is that there is a great degree of variability in people with ASDs on virtually all brain measures (Gage et al., 2009), just as heterogeneity is observed in features of the behavioural presentation and symptoms of affected individuals (see Waterhouse, 2013). However in spite of these caveats, it is apparent that the growing body of evidence indicates atypical cortical lateralization in people with ASDs, with a number of key left hemisphere language regions showing reduced or reversed asymmetry (see Figure 1). The present data do not, however, shed light on whether these atypical patterns of lateralization are present from birth or reflect an adaptation to abnormal cortical development. Further study is clearly needed to determine whether structural asymmetry prenatally is a predictor of later outcomes, offering the potential to increase intervention efficacy.
Figure 1  Regions indicating atypically reduced left hemisphere structural asymmetry in people with ASDs (dashed lines ---- indicate connective fibre tracts). Brain drawing courtesy Michael Lindell.

Handedness

As a highly visible manifestation of lateralization, handedness has long been argued to offer insight into underlying patterns of cortical lateralization. Broca (1865) was famously the first to suggest that language was lateralized in the brain, and proposed an intimate relationship between the lateralization of speech and handedness: right handers have left hemisphere control of articulate language, whereas left handers have right-lateralized speech (see Elias, 1991, 1993). Whilst such a direct, one-to-one relationship between handedness and speech lateralization has since been repudiated, research confirms that there is a strong link between handedness and language lateralization. Ninety-six percent
of strong right handers have left lateralized speech, dropping to 85% of mixed-handers, and 73% of strong left handers (Knecht, Dräger, Deppe, Bobe, Lohmann, et al., 2000).

This relationship between handedness and cortical lateralization for speech is important: theoretically, language disorders and anomalous handedness may both reflect atypical cerebral lateralization. According to Leask and Crow (2001), stronger lateralization is linked with earlier acquisition of words, and stronger dominant hand skill predicts increasing verbal ability. Given the strength of the relationship between well-established cortical lateralization, clear hand preference, and strong language ability, one would anticipate poorer outcomes for those with anomalous cerebral dominance and atypical handedness. And indeed, research confirms that an increased incidence of left and mixed handedness is observed in a number of different disorders and learning disabilities, including epilepsy, schizophrenia, and Down syndrome (e.g., Flor-Henry, 1983; Batheje & McManus, 1985).

It is thus not surprising that both left handedness and mixed handedness are observed more frequently in people with ASDs than in the general population (e.g., Satz, Green, & Lyon, 1989). In the general population, atypical handedness is, indeed, atypical: approximately 8% of the typically-developing population is left handed (e.g., Seddon & McManus, 1993), and 3% to 4% is mixed-handed (e.g., Satz, Nelson, & Green, 1989). However research indicates a marked increase in atypical handedness in people with ASDs, with an 18-57% incidence of left handedness, and a 17-47% incidence of mixed handedness (e.g., Fein, Humes, Lucci, & Waterhouse, 1984; Satz, Soper, Orsini, Henry, & Zvi, 1985; Soper, Satz, Orsini, Henry, Zvi, & Shulman, 1986; Lewin, Kohen, & Mathew, 1993; Dane & Balci, 2007), again implying atypical cortical organization in ASDs.

For example, when Cornish and McManus (1996) used a performance-based task (pegboard) to assess the handedness of children with ASDs, children with learning
disabilities, and typically-developing children, they found that left handedness was five times as frequent in children with ASDs as in typically-developing children, and twice as common in this former group as in children with learning disabilities. Though their assessment of handedness was far less stringent (i.e., hand used to write and throw a ball was taken as the dominant hand), Dane and Balci (2007) similarly reported a marked increase in left handedness in children with ASDs (56.8%) compared with controls (10%).

Though a large number of investigations have reported an increased incidence of left handedness in people with ASDs in comparison to controls (e.g., Fein et al., 1984; Cornish & McManus, 1996; Colby & Parkinson, 1977), not all investigations have found such a relationship. For example, Boucher (1977) reported no difference in the incidence of left handedness for children with ASDs compared to controls, however as she notes, this absence of difference likely results from the small sample size. Barry and James (1978) similarly reported no difference in the frequencies of left, right, and mixed handedness for children with ASDs (4–18 years) and either intellectually-impaired controls matched on sex, age, and IQ, or typically-developing children matched on sex and age alone. They did, however, note that the children with ASDs were less likely to favour their dominant hand than were children in either of the control groups, consistent with the notion of reduced lateralization.

Left handedness is not the only atypical hand preference observed more frequently in children with ASDs: an increase in ambiguous/mixed handedness is also evident, with estimates ranging from 17% to 47% of this population (e.g., Tsai, 1982; Colby & Parkinson, 1977; Campbell, 1978; Hauser, DeLong, & Rosman, 1975; though see Barry & James, 1978; Boucher, 1977). For example, Dane and Balci (2007) found a markedly higher incidence of mixed handedness in children with ASDs (32.4%) in comparison with typical controls (0%). The absence of mixed handers in the group likely reflects the age of
the sample (5 – 20 years); in typical development, handedness is normally established by
the time children start school (e.g., Gudmundsson, 1993), highlighting the anomalously
high incidence of mixed handedness in people with ASDs (mixed handedness incidence
does not decrease with age in people with ASDs, Tsai, 1983).

Intriguingly, McManus, Murray, Doyle, and Baron-Cohen (1992) found that
ambiguous handedness (i.e., inconsistency of hand preference within a task) was more
common in children with ASDs in comparison with both an intellectually-impaired and a
typically-developing control group, even when chronological age and mental age were
taken into account. However other investigations (e.g., Cornish & McManus, 1996; Satz et
al., 1989) have reported comparable levels of ambiguous handedness in groups of
individuals with ASDs and learning-disabilities.

Mixed hand preference has long been thought to reflect a failure to establish cerebral
dominance, manifesting in cognitive deficit (e.g., Orton, 1937; Delcato, 1966; Crow,
Crow, Done, & Leask, 1998; though see Pipe, 1988). Data examining the cognitive
consequences of mixed hand preference in people with ASDs are concordant. For
example, Tsai (1983, 1984) confirmed a clear relationship between mixed handedness,
greater cognitive impairment, and poorer functional outcomes. Examining both children
(Tsai, 1984) and adults (Tsai, 1983) with ASDs, Tsai found that people with a clear hand
preference, whether left or right, had better functional outcomes than mixed handers.
Mixed handed people with ASDs exhibited lower functioning scores for language,
intelligence, and visuospatial ability, than either left or right handed people with ASDs,
consistent with greater cortical abnormality in the mixed handed group. Hauck and
Dewey's (2001) data are consistent, confirming that children with ASDs who have an
established hand preference display superior performance on motor, language, and other
cognitive tasks than children without a clear preference.
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Soper et al. (1986) similarly reported poorer intellectual outcomes for ambiguous/mixed handed people with ASDs in comparison with left and right-handed people with ASDs. The poorer outcomes for mixed handers were again postulated to reflect bilateral cerebral pathology resulting from early brain injury. Given such findings, Tsai (1983) proposed that an established hand preference by age five could be used as a predictor of better outcomes in children with ASDs. Both Hauck and Dewey's (2001) and Soper et al.'s (1986) studies support this proposition.

Data assessing the relationship between early language disturbance and handedness in children with ASDs are concordant in suggesting that atypical dominance is linked to poorer functional outcomes. Escalante-Mead, Minshew, and Sweeney (2003) compared lateral preferences of children with ASDs who had a history of early language disturbance, children with ASDs who had normal early language skills, and typically-developing controls. The data confirmed that the children with ASDs who had a history of language disturbance had less well-established lateral preferences than the children with ASDs who had normal early language, and this group in turn had a reduced rate of established hand preference in comparison to the typically-developing controls. As such, these data confirm a pattern of inconsistent cerebral dominance in ASDs, and moreover, are consistent in suggesting that this atypical dominance may underlie the disordered language that presents so commonly.

In sum, the data from handedness studies in people with ASDs suggest that atypical handedness, whether left handedness or ambiguous/mixed handedness, occurs at a much higher incidence than that observed in the general population. Given that there is a close relationship between handedness and cerebral lateralization, such data appear consistent with the structural research in suggesting a failure of normal lateralization in the brains of individuals presenting with ASDs.
**Functional Lateralization**

The presence of structural atypicalities in the brains of people with ASDs does not, in and of itself, necessitate concomitant atypicalities in terms of functional activation. However, just as the data from studies examining both brain structure and handedness in people with ASDs indicate decreased lateralization, data from functional investigations implicate anomalous lateralization. Numerous studies have demonstrated reduced left hemisphere activity during language-based tasks in people with ASDs, both during language production (e.g., Kleinhaus, Müller, Cohen, & Courchesne, 2008), and language perception (e.g., Frye & Beauchamp, 2009; Ting Wang, Lee, Sigman, & Dapretto, 2006). Indeed, some have found the leftward asymmetry noted in controls reversed to such an extent that it produces a right hemisphere bias in functional activation in people with ASDs (e.g., Dawson, Finley, Philips, & Galpert, 1986; Flagg, Oran Cardy, Roberts, & Roberts, 2005).

Early investigations of functional lateralization made use of inferential behavioral techniques, such as dichotic listening, to infer patterns of hemispheric dominance for language perception. The dichotic listening task presents two different stimuli simultaneously to the left and right ears; participants are asked to report what they heard. A bias toward information from the right ear is taken as evidence of left hemisphere dominance for the task, whereas a left ear bias indicates right hemisphere dominance, given the predominant contralateral cortical control of audition. Using the dichotic listening technique Blackstock (1978) found that typically-developing children had a right ear preference for verbal stimuli and a left ear preference for music; in marked contrast, children with ASDs exhibited a left ear (i.e., right hemisphere) preference for both verbal and musical stimuli, indexing anomalous language lateralization. In a similar vein, Prior
and Bradshaw (1979) reported that a significant number of children with ASDs (8 – 13 years) showed a left ear (i.e., right hemisphere) advantage for language stimuli in their dichotic listening tasks, contrasting with the right ear (i.e., left hemisphere) advantage characteristic of typically-developing controls.

In contrast however, Arnold and Schwartz's (1983) dichotic listening investigation failed to find a difference in ear preference for discriminating stop consonants between children with ASDs (6 – 14 years) and typically developing controls. While the authors suggest that both groups showed a right ear (i.e., left hemisphere) preference, inspection of scores suggests that both the typically developing and the ASDs participants showed a lack of asymmetry: participants with ASDs had a mean ear advantage score of 0.089 whereas the typically developing participants' mean was higher (0.132), though not significantly so. Given that ear advantage scores range from -1.0 to +1.0 (negative scores indicating a left ear preference; positive scores indicating a right ear preference), the observed means of 0.089 (ASDs) and 0.132 (typically-developing) clearly fall in the 'mixed' range. The difference in finding is likely attributable to the small sample tested by Arnold and Schwartz (eight participants with ASDs) compared with Prior and Bradshaw's (1978) previous investigation (19 participants with ASDs). Had Arnold and Schwartz tested a sample sufficient to power their analysis, one would anticipate that the difference between groups would achieve significance, indexing reduced asymmetry in the ASD group. Replication is needed to confirm this speculation.

The advent of neuroimaging techniques, such as electroencephalography (EEG), functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and late field magnetoencephalogram (MEG), has allowed researchers a more direct window into cortical activity by measuring changes in cerebral metabolism whilst participants perform different cognitive tasks. Whereas typically developing adults show greater left
hemisphere activity in response to linguistic stimuli (e.g., Stefanatos, Joe, Aguirre, Detre, & Wetmore, 2008), investigations using neuroimaging techniques have again confirmed anomalous patterns of cerebral lateralization in people with ASDs. For example, EEG studies indicate reversed lateralization in children with ASDs, showing right rather than left hemisphere dominance for language tasks, consistent with previously-reported behavioral findings (e.g., Dawson, Warrenburg, & Fuller, 1982). Recent data indicate that this anomalous lateralization is evident very early in life, with Seery, Vogel-Farley, Tager-Flusberg, and Nelson's (2013) electrophysiological investigation demonstrating that infants (6 – 12 months) at high risk of developing autism fail to show the strongly lateralized response to speech sounds exhibited by low risk control infants.

The maturational trajectories of language lateralization in children with ASDs and typically-developing children (8-17 years) are also strikingly different (Flagg, Oram Cardy, Roberts, & Roberts, 2005). Flagg et al.’s MEG study used simple vowel stimuli and a passive auditory presentation paradigm; results indicated that initially bilateral activation patterns become increasingly left lateralized as typically-developing children age, but increasingly right lateralized as children with ASDs grow older. Though the sample size was very small (6 children in each group), these data indicate anomalous cortical responses to basic verbal stimuli in children with ASDs, consistent with "an absence of LH (left hemisphere) cortical specialization for language, with possible dominance of RH (right hemisphere) language area homologies instead" (Flagg, et al., 2005, p.85).

Recent research by Eyler, Pierce, and Courchesne (2012) is congruent, indicating a deficient left hemisphere response to speech sounds (see also Redcay and Courchesne, 2008). Like Flagg et al. (2005), Eyler et al. (2012) used a passive auditory presentation paradigm but in this case, the stimuli were bedtime stories (i.e., natural language rather than simple vowels), presented to children (1 – 4 years) during natural sleep. The study
adopted a prospective design, allowing the researchers to target infants and toddlers at high-risk for ASDs, examining patterns of cortical activation in individuals who they later confirmed to have ASD diagnoses. fMRI results indicated an attenuated left hemisphere response to speech sounds, accompanied by an abnormal increase in right temporal activation, in toddlers with ASDs; typically-developing toddlers showed the expected dominant left-lateralized activation. Akin to Flagg et al.'s findings, the pattern of abnormal lateralization in ASDs increased with age, suggesting that anomalous cortical activation evident in the brains of infants with ASDs become more pronounced over toddlerhood/early childhood and indeed, "may last across the lifetime" (Eyler et al., 2012, p.956).

Studies investigating sentence processing in people with ASDs again highlight atypical lateralization. Müller, Behen, Rothermel, Chugani, Muzik, et al.'s (1999) pilot PET investigation was the first to compare functional activation in adults with high-functioning ASDs and controls during a sentence processing task. As anticipated, individuals with ASDs showed reduced left frontal activation (Brodmann area 46) in comparison to controls. This pattern of reduced left hemisphere frontal activation in ASDs has since been confirmed by Just, Cherkassy, Keller, and Minshew (2004), though in this case, reduced fMRI activity in Broca's area was accompanied by increased activation in Wernicke's area (Brodmann area 21, 22), akin to the findings for single words reported by Harris et al. (2006). Although Anderson, Lange, Froehlich, DuBray, Druzgal, et al.'s (2010) phrase-recognition task prompted similar fMRI activation magnitudes in Broca's area in people with ASDs and controls, results indicated reduced left insular activation in people with ASDs, and increased activation in the right hemisphere homologue of Wernicke's area. Anderson et al.'s study thus suggests greater bilateral activation during
language processing in people with ASDs, again offering evidence of atypical language lateralization.

Harris, Chabris, Clark, Urban, Aharon, et al. (2006) used fMRI to examine semantic processing activation patterns in adult males with ASDs. Whereas semantic processing activated Broca's area (Brodmann area 45) in control participants, perceptual processing of the same stimuli did not. In contrast, participants with ASDs showed less activation in Broca's area during the semantic processing task and more activation in the left middle temporal gyrus (Brodmann's area 21). Critically, the semantic and perceptual tasks prompted similar fMRI responses in Broca's area for people with ASDs, indicating an abnormal lack of specificity in activation. Importantly, this aberrant activation did not impact upon behavioral performance (i.e., reaction times, error rates), highlighting the fact that atypical patterns of neuronal activation do not, of necessity, imply poorer performance. Instead, the data suggest that though alternate neural networks are engaged by high-functioning adults with ASDs, there is more than one way to perform a semantic evaluation task.

The functional imaging data are in line with the previously-reported structural imaging data in implicating an intimate relationship between atypical lateralization and language impairment: more atypical lateralization is linked to greater language impairment. For example, Dawson Finley, Philips, and Galpert (1986) used cortical evoked responses to examine activation in response to auditory linguistic stimuli in children with ASDs (6 – 18 years). Though one must be cautious in drawing conclusions about lateralization from evoked responses data (the technique having exquisite temporal, but poor spatial, resolution), results indicated that 68% of children with ASDs had a reversed (i.e., right hemisphere) asymmetry in response to the linguistic stimuli. Moreover, the children with ASDs who had more disordered language were more likely to have a reversed pattern of
activation than those children with less impaired language (see also Dawson, Finley, Philips, & Lewy, 1989).

Coffey-Corina, Padden and Kuhl's (2008) event related potential (ERP) data are congruent, indicating that lower functioning children with ASDs (1–3 years) show stronger right hemisphere lateralization to known and unknown words than either higher functioning children with ASDs or typically developing controls. Whereas the brains of lower functioning children with ASDs showed differences in response between known and unknown words across multiple right hemisphere electrode sites, indicating pronounced right hemisphere lateralization of language response, the brains of higher functioning children with ASDs and typically developing controls exhibited a focussed response, distinguishing between known and unknown words at a single left hemisphere parietal electrode site. As such, these data appear consistent with the notion that more atypical lateralization is linked to poorer outcomes.

Part of the reason why people with ASDs exhibit language impairments may lie in the fact that their brains show an attenuated response to phonetic stimuli (e.g., Dawson, Finley, Phillips, Galpert, & Lewy, 1988). For example, when Dawson et al. (1988) compared P3 ERP responses to phonetic (Da) and musical (piano chord) stimuli in children with ASDs (8–19 years) and typically developing controls, there was no difference in P3 amplitude in either hemisphere in response to the musical stimuli (the P3 component of the ERP waveform is associated with the engagement of attention; Polich, 2003). However in response to phonetic stimuli children with ASDs evidenced significantly reduced P3 amplitudes at left hemisphere sites in comparison with the typically developing group. The fact that this difference in response was specific to phonetic stimuli suggests that the issue is restricted to language, and not a generalised auditory attention problem.
In a similar vein, research indicates that the brains of people with ASDs fail to respond differentially to speech and environmental sounds (Gervais, Belin, Boddaert, Leboyer, Coez, et al., 2004). This finding is in marked contrast to controls who demonstrated selective bilateral superior temporal sulcus activation in response to voices but not environmental sounds. The fact that the brains of people with ASDs did not distinguish between speech and general environmental sounds could reflect either a bottom-up or top-down problem: as Groen et al. (2008) suggest, the ASD group may have a bottom-up sensory impairment, or they may have a top-down attentional bias towards non-speech sounds which, in turn, leads to further language impairment.

To tease apart top-down and bottom-up influences, Boddaert, Belin, Chabane, Poline, Barthelemy, et al. (2003) used PET to measure patterns of activation in response to pre-linguistic sounds that have the acoustic structure of speech, but lack any form of semantic language content. As such, these prelinguistic stimuli allow assessment of brain responses to prelinguistic auditory processing (bottom-up perceptual processing) rather than speech recognition (top down semantic processing). Their data demonstrated opposing patterns of lateralization in the ASD and control groups, with people with ASDs showing greater right frontal activation, and reduced left temporal activation, than control participants. As these opposing patterns of lateralized activation were generated in response to pre-linguistic sounds, thus minimizing the contribution of top-down processing, the data suggest the presence of a bottom-up, rather than top-down, deficit in people with ASDs. Such a deficit compromises encoding, potentially catalysing the anomalous lateralization that characterises the brains of people with ASDs: if a bottom-up failure in perceptual processing precludes children with ASDs from adequately perceiving linguistic stimuli, this will adversely impact the pattern of stimulation delivered to the brain, potentially interfering with the emergence and/or establishing of language lateralization.
The neuroimaging data examining language lateralization in people with ASDs are somewhat heterogenous, but given the heterogeneity endemic to these conditions (see Waterhouse, 2013) and also the variation in specific participant groups tested across studies, this is perhaps to be expected. In general, however, existing findings appear contiguous with the structural imaging and handedness data: people with ASDs show atypical functional lateralization, with reduced left hemisphere and/or reversed patterns of cortical activation in response to linguistic stimuli. The data also suggest that abnormalities in functional organization of language may directly contribute to language impairment (Stefanatos & Baron, 2011), again in parallel with the structural findings. As Lindell, Notice, and Withers (2009) note, greater right hemisphere activation during language processing in people with ASDs could either be the cause or the result of abnormal structural asymmetry. If the volumetric asymmetry is present at birth, it may catalyse greater right hemisphere involvement in language processing, with pathological structure prompting atypical functional activation. Alternately, atypical structural asymmetry may develop in response to experience, with right hemisphere language homologues becoming enlarged to compensate for left hemisphere deficiencies. Whilst either possibility is plausible, the answer at present is unclear; further research is required to elucidate the cause and developmental trajectory of structural and functional atypicalities evident in the brains of people with ASDs.

Conclusions and Future Directions

Research evidence from the structural, functional, and behavioral investigations reviewed here converges to indicate a pattern of atypical lateralization in people with ASDs. As discussed, such a conclusion is far from surprising, given that language is typically a highly lateralized function and that language impairment is central to diagnosis.
and prognosis in ASDs (Herbert et al., 2002). Consequently, one would anticipate that people with reduced or reversed language lateralization would exhibit language impairments. The research reviewed suggests that precisely such a pattern of cortical and behavioral atypicality is evident in individuals with ASDs. Importantly, the present review emphasizes that atypical lateralization is not only common in people with ASDs, but is intimately related to language impairment; a number of investigations converge to indicate that more atypical structural (e.g., De Fossé et al., 2004) and functional asymmetries (e.g., Dawson, et al., 1986), and more ambiguous hand preferences (e.g., Hauck & Dewey, 2001), implicate greater language impairment.

Based on the findings of the research reviewed, we have developed a model of the relationship between reduced structural lateralization, reduced functional lateralization, and language impairment in ASDs (see Figure 2). In the model we have suggested that initial genetic and/or environmental atypicality alters the developmental process of cortical lateralization, manifesting in reduced structural lateralization and mixed handedness. The experience of mixed handedness is proposed to effect further direct reductions in structural lateralization: habitual use of one hand leads to increases in dendritic branching and cortical activation in the contralateral hemisphere, consolidating lateralization, whereas mixed handers' lack of hand preference prompts more bilateral activation, further reducing structural lateralization (see Provins, 1997, for review of the roles of genetic and environmental factors in lateralization).
Figure 2: A model of the relationship between reduced structural lateralization, reduced functional lateralization, and language impairment in ASDs.

The model proposes that in ASD, atypical structural lateralization affects key language regions and the connections between them (see Figure 1 for overview), adversely influencing the brain's response to language. Crucially, our model proposes that the relationship between reduced structural lateralization and atypical functional lateralization for language in ASD is bidirectional: reduced structural lateralization of the inferior frontal and posterior superior temporal regions attenuates left hemisphere responses to speech, and the reduced cortical response to speech, in turn, leads to further atypicalities in structural lateralization. Similarly, reduced structural lateralization of the planum temporale reduces attention to speech, and this reduced attention further consolidates...
atypical structural lateralization in the region. Language learning in people with ASD is altered as a direct consequence of the reduced left hemisphere response to language, reduced left hemisphere connectivity, and reduced attention to speech. The model thus proposes that the language impairments observed in people with ASD stem from an alteration in language learning which, in turn, results from reduced structural and functional lateralization. In addition, we suggest that the relationship between language impairment and language learning is bidirectional, recognising that language impairment is not only a result of altered language learning but also a contributor: language impairment in itself compromises learning of the language system.

The relationships between reduced structural and functional lateralization proposed in the model are consistent with the research reviewed. However further research is needed to test the proposals and predictions of the model, including investigating the genetic and/or environmental factor(s) argued to catalyse reduced structural lateralization and mixed handedness, and establishing whether there is indeed a direct relationship between reduced functional lateralization and altered language learning. As such, there are a number of promising opportunities for future investigation.

The 'chicken or egg' question of whether structural atypicalities lead to abnormal function, or functional atypicalities promote abnormal structure, is yet to be answered. In the proposed model we have suggested a bidirectional relationship such that initial structural atypicalities lead to functional atypicalities which, in turn, further promote anomalous structural lateralization. For example, it seems plausible that a lack of attention to, and interest in, the speech of others during early development may lead to aberrant connectivity within the left hemisphere fronto-temporal language regions. Along this line, Bigler et al. (2007) question whether attentional biases and repetitive behaviours early in life allow regions like the superior temporal gyrus to appear normal in size, but be
functionally impoverished due to a relative paucity of experience-based connectivity and neural pruning. Such a question cannot be answered using a cross-sectional paradigm; longitudinal research is clearly required to gain a richer understanding of causation and lateralization in ASDs.

Another issue, also unlikely to be answered using traditional cross-sectional methods, pertains to heterogeneity among ASDs. While we have explicitly acknowledged the marked variability present across all areas pertinent to ASDs, highlighting cognition and language as being of particular relevance to this topic, we have necessarily restricted the extent to which we have discussed heterogeneity, given that the findings reviewed here have come from a time when the focus has been predominantly on finding unifying theories or principles for ASDs, rather than actively targeting individual variation. Waterhouse (2013) provides an important and very thorough consideration of the issue of heterogeneity, and similar consideration within the context of the current topic presents an important direction for future research into ASDs, including but not limited to understanding cognitive phenotypes and their neural bases.

To more comprehensively understand the relationship between structural and functional abnormalities with respect to language in ASDs, researchers should follow a group of at-risk individuals from birth through to the possible point of diagnosis in early childhood, and beyond, into adulthood. By longitudinally investigating the relationship between brain structure and behavioral function using a series of imaging, neuropsychological, and cognitive tests, important light could be shed on the relative contributions of nature and nurture to emerging patterns of lateralization in ASDs. Such a design, allowing for the separation of subgroups of individuals at similar initial risk for ASDs, but with different developmental trajectories and outcomes (i.e., an ASD, broader developmental/language delays without an ASD, and typical development; e.g., Clifford,
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Hudry, Elsabbagh, Johnson, & Charman, 2013), would afford insights into the relationships between cortical atypicalities and language impairments in the context of developed ASDs and also outside of this outcome. Furthermore, adopting an individual-differences approach within such a prospective endeavour would allow researchers to directly investigate arising heterogeneity in each of the relevant factors – neural structures, functional behaviour, and symptomatic presentation – potentially affording greater insights into the mechanisms at play.

Such longitudinal research will also assist in testing the predictions of the proposed model, confirming the extent to which the language deficits prominent in ASDs stem from structural abnormality, functional abnormality, or some combination of the two. Groen, Zwiers, van der Gaag, and Buitelaar (2008) suggest that the development of language-related cortex follows a different trajectory in ASDs, possibly resulting from reduced left hemisphere dominance. If, as we have proposed in the model, atypical structural asymmetries result prenatally from a genetic and/or environmental atypicality and are thus present from birth in children who go on to be diagnosed with an ASD, their presence can be used to aid the implementation of early and vigorous intervention. As Rapin and Katzman (1998) suggest, early educational intervention that addresses language issues at a time of rapid development and enhanced brain plasticity has the potential to effect dramatic improvements. Thus the need to identify such early biomarkers is urgent.

Familial research offers a promising avenue for investigation, given that there is an increased rate of language impairment and also sub-threshold traits akin to ASD-type symptoms in the relatives of people with ASDs, suggesting clear genetic contribution (Herbert & Kenet, 2007). As patterns of cerebral asymmetry are genetically influenced (e.g., Hyatt & Yost, 1998), and emerge very early in fetal development (e.g., Sun, Patoine, Abu-Khalil, Visvader, Sum, et al., 2005), atypical asymmetries evident prenatally may be
an endophenotype for ASDs, as proposed by the model. If so, this offers the potential for early identification of substantive individual risk for an ASD, early diagnosis thereof, and thus, earlier intervention. There are a number of potential candidates. For example, Eyler et al.’s (2012) data indicate that a failure of left temporal activation in response to speech is evident in children with ASDs from one year of age, suggesting that this is "an early emerging and fundamental property of autism", (p.949), pointing toward a potential neurofunctional biomarker. The need for such biological markers of ASDs is great, given the inefficiency of, and difficulties with, basing early diagnosis on behavioral symptoms (Groen et al., 2008). At present, the search for biomarkers that distinguish people with ASDs from those developing typically is in its infancy; any biomarker must demonstrate highly reliable classification accuracy to have clinical merit. Whilst showing suggestive promise, potential biological measurements are not yet clinically adequate (Elsabbagh et al., 2012; Lange et al., 2010), hence the importance of further investigation to more precisely delineate biomarkers stemming from the structural and functional atypicalities in lateralization linked with ASDs. Such investigation may facilitate earlier identification of individuals at risk for an ASD, earlier diagnosis of such a condition as it is emerging, and thus the earlier implementation of intervention to maximise positive outcomes for people with ASDs.
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REFERENCES


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