Handedness in Children with Autism Spectrum Disorder

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Abstract
The left hemisphere is usually predominant in manual skills and language, suggesting a link between hand dominance and language. Studies of autism spectrum disorder show atypical handedness; however, few have examined language-handedness associations. Handedness, assessed by task performance, and standardized receptive and expressive language tests were completed in 110 autism spectrum disorder children (96 boys; M age = 8.3 years, SD = 3.8) and 45 typically developing children (37 boys; M age = 8.6 years, SD = 4.3), 3 to 17 years of age. The autism spectrum disorder group had a lower handedness score (was less strongly lateralized) than the control group. In the autism spectrum disorder group, there was a small effect of handedness on language; right-handers had better language than non-right-handers. Results suggest poorer language prognosis may be associated with left- or mixed-handedness in autism spectrum disorder.

Keywords
autism, handedness, language, laterality

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Introduction

One of the most prominent asymmetries found in humans is that of hand preference, with the majority of the population, about 90%, being right-handed. Although rates of right- and left-handedness have varied throughout history and across geographical areas, right-handers have consistently been predominant (McManus, 2009). The exact determinants of this asymmetry remain unknown; however, there are likely many genes, as well as environmental factors, which play a role.

Autism spectrum disorder (ASD) is a neurodevelopmental disorder defined by impairments in social interaction and communication, with the presence of restricted interests or repetitive behaviors (American Psychiatric Association, 2013). Although not considered part of the diagnostic criteria, differences in motor functions are often noted in people with ASD (Cattaneo et al., 2007; Cook, Blakemore, & Press, 2013; Fabbri-Destro, Cattaneo, Boria, & Rizzolatti, 2009; Mari, Castiello, Marks, Marraffa, & Prior, 2003). Similarly, differences in handedness have been found. Decreased degree of right-handedness in ASD has been found (Cornish & McManus, 1996; Escalante-Mead, Minshew, & Sweeney, 2003; Hauck & Dewey, 2001; McManus, Murray, Doyle, & Baron-Cohen, 1992). Several studies, using different methodologies, have also shown increased rates of left-handedness or increased rates of non-right-handedness in ASD relative to their family members, typically developing controls, or the general population (Colby & Parkison, 1977; Dane & Balci, 2007; Gillberg, 1983; Lewin, Kohen, & Mathew, 1993; Soper et al., 1986; Tsai, 1982; for review, Lindell & Hudry, 2013). Cornish and McManus (1996) found that typically developing children were more right lateralized and more consistent in their hand preference when measured multiple times, relative to children with ASD. Another study showed that children with ASD tended to have more mixed-handedness, but that those who had a definite hand preference performed better on motor, language, and cognitive tests than those who did not (Hauck & Dewey, 2001). In their review article, Lindell and Hurdy (2013) concluded that individuals with ASD had more mixed hand preferences.

Another prominent asymmetry in humans is that of language functions, with the left hemisphere playing a predominant role in most healthy people. There is also evidence of a close association between language functions and handedness (for review, Ocklenburg, Beste, Arning, Peterburrs, & Gunturkun, 2014). In more than 95% of right-handers, the left hemisphere plays a predominant role, relative to the right, in language functions (see Foundas, 2001; Pujol, Deus, Losilla, & Capdevila, 1999; Springer et al., 1999). Thus, in the majority of the population, the left hemisphere plays a dominant role in both manual skills and language functions. Left-handers are less likely than right-handers to have left lateralized language; however, left-handers are not the mirror image of right-handers with respect to this function, as about 70% of left-handed adults have language functions lateralized to the left hemisphere (Jorgens, Kleiser, Indefrey,
Evolutionary hypotheses have suggested that this association between handedness and language may be related to early forms of communication, which were gesture-based (for review, Corballis, 2003). Studies of infants and toddlers have shown associations between pointing and language ability (for review, Cochet, 2015). One study in infants found that those who pointed with their right hand understood and produced more words than infants who did not point with their right hand (Esseily, Jacquet, & Fagard, 2011). Another study found an increase in right-handed pointing during the lexical spurt (Cochet, Jover, & Vauclair, 2011). Similarly, Vauclair and Cochet (2013) demonstrated a right-hand preference for pointing in toddlers, and this was correlated with better language in a subgroup with relatively advanced language. These studies, however, did not find a relationship between handedness and language, suggesting separate development of communicative versus non-communicative manual actions, at least before age 3 (Cochet, 2015). However, in 4 to 5 year olds, Gonzalez, Li, Mills, Rosen, and Gibb (2014) showed that children who had more of a right-hand preference for picking up food items to eat had enhanced differentiation of the “s” and “sh” sounds. Another study of a large sample of school-aged children (7–12 years) found that right-handers performed significantly better than left-handers on language tests (Natsopoulos, Kiosseoglou, Xeromeritou, & Alevriadou, 1998). The close proximity of Broca’s area, a critical language region, and motor regions suggests that these frontal regions may be important in the link between handedness and language. In addition to being involved in semantic functions (Démonet et al., 1992; Zatorre, Meyer, Gjedde, & Evans, 1996) and syntactic processing (Dapretto & Bookheimer, 1999; Embick, Marantz, Miyashita, O’Neil, & Sakai, 2000), the inferior frontal gyrus and adjacent regions are involved in gesture production (Willems & Hagoort, 2007) and the posterior portion of this region, the pars opercularis, contains motor association cortex (Hynd & Cohen, 1993; Mesulam, 2000), as well as mirror neurons.

Language and communication difficulties are a core feature of ASD, and language abilities can range from a complete lack of functional language to above average ability on standardized tests (Tager-Flusberg et al., 2005). A number of studies have demonstrated atypical language organization in ASD. One of the most consistent findings of neuroimaging language studies is reduced or reversed left-lateralized activation during language tasks in individuals with ASD relative to controls (Boddaert et al., 2003; Boddaert, et al., 2004; Gervais et al., 2004; Knaus, Silver, Lindgren, Hadjikhan, & Tager-Flusberg, 2008; Müller et al., 1998, 1999). Very few studies, however, have explored the association between language and handedness in ASD. Escalante-Mead et al. (2003) examined handedness in adolescents and adults with ASD with impaired early language development and those with normal early language, based on the Autism Diagnostic Interview-Revised (ADI-R). They found those with early
language deficits had more atypical (mixed) hand dominance than typically developing individuals, as well as compared to those with ASD with normal early language acquisition, suggesting an association between handedness and language deficits within ASD. In a review of the fMRI literature and meta-analysis of a few studies, however, Preslar, Kushner, Marino, and Pearce (2014) concluded that in ASD, there is a decrease in laterality relative to controls, but that handedness is not a moderating factor. They note, however, that most studies only used self-report to define handedness and many only included right-handers, with more studies necessary to further examine this relationship.

Although the development of handedness may begin in infancy, several studies have demonstrated that the direction of handedness is generally established by about 3 years of age, with changes in the degree of handedness occurring until school age. A study of 3 to 9 year olds, using a performance inventory, found that handedness direction was established by 3 year olds, but that the degree of handedness increased in 3 to 7 year olds (McManus et al., 1988). Similarly, Hill and Khanem (2009) showed that children 4 to 5 years old had weaker hand preference than older children, 8 to 11 years, with no differences between the groups in writing hand. Another study demonstrated that the number of midline crossings increased from 3 to 10 years and younger children (3–4 years) crossed the midline less frequently than children over seven years (Carlier, Doyen, & Lamard, 2006). This indicates that older children are more lateralized than younger, as those who frequently cross the midline are more strongly right- or left-handed and crossing values correlated with handedness scores. When examining pegboard performance, a study found that 5 to 6 year olds had a greater performance difference between hands (favoring the right) than 3 to 4 year olds (Scharoun & Bryden, 2015). Not all studies, however, have found these age-related differences. Gonzalez, Flindall, and Stone (2015) found no differences in children (2–11 years) compared to young adults (17–28 years) on a handedness questionnaire. They did not, however, compare the younger to the older group of children. When examining grasping measures, they did not find differences between children 2–4, 5–8, or 9–11 years. According to a review article by Scharoun and Bryden (2014), younger children, 3–5 years, have weaker and less consistent hand preferences whereas older children, 7–10 years, demonstrate stronger, more consistent hand preferences, which are driven by experience, learning, and practice and a period of motor skill refinement. Age-related differences in handedness have not generally been examined in ASD. Cornish and McManus (1996) examined a group of young children, 3–5 years, and older children, 11–13 years, and only found age effects in consistency, with younger children being less consistent than older children in both groups.

The current study was designed to examine hand preference in a large, modern sample of children and adolescents with ASD (n = 110; ages 3–17 years) compared to an age-matched group of typically developing children.
and adolescents \((n = 45)\). Another aim of the present study was to investigate the relationship between handedness and language ability. Given the large age range of the study, the effects of age were also examined. Based on previous findings involving smaller samples with ASD, it was predicted that the ASD group would have reduced right-handedness and contain more non-right-handers (mixed- or left-handers) relative to the typically developing group. Based on previous studies of young and school-aged children (Gonzalez et al., 2014; Natsopoulos et al., 1998), it was hypothesized that within the typically developing group, right-handers would perform better on language tests than non-right-handers. Most ASD studies have excluded left-handers or have not examined right- and left-handers separately, however, based on a few prior studies (Escalante-Mead et al., 2003; Knaus, Kamps, & Foundas, unpublished), it was predicted that in ASD, poorer language skills would be associated with atypical (left- or mixed-) hand preference. Studies of typically developing children have generally shown that young children have weaker hand preferences; therefore, it was predicted that younger children (3–5 years) would have reduced right-handedness compared to school-aged children (6–17 years). The effect of age on handedness has not been examined in ASD; however, it may be that this group is more delayed in establishing consistent handedness. Therefore, it was hypothesized that the younger children in the typically developing group and ASD children would be more similar; in addition, ASD children in the older group would have reduced right-handedness compared to controls.

**Method**

**Participants**

Participants included 110 children with ASD (96 boys, 14 girls; \(M\) age = 8.3 years, \(SD = 3.8\) ) and 45 typically developing children (37 boys, 8 girls; \(M\) age = 8.6, \(SD = 4.3\)), overall age range 3–17 years. For ASD participants, diagnosis was based on DSM-IV criteria (American Psychiatric Association, 1994) using the ADI-R (Rutter, Le Couteur, & Lord, 2003) and the Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, DiLavore, & Risi, 1999). In addition, an expert clinician (JK) confirmed that all participants met criteria for ASD. Typically, developing participants had no history or current diagnosis of developmental, learning, psychiatric, or neurologic disorders and no immediate family members with an ASD diagnosis.

Parents and participants were informed of the procedures and parents gave written consent prior to the child’s participation in the study. Children who were able, also provided written assent prior to participation. All data in this manuscript were collected in compliance with the Louisiana State University Health Sciences Center and Children’s Hospital Institutional Review Boards.
Standardized tests

Receptive and expressive language were assessed with subscales of the Mullen Scales of Early Learning (Mullen, 1995) or the Oral and Written Language Scales (OWLS; Carrow-Woolfolk, 1995). One participant with ASD did not complete language testing and one ASD participant only completed the receptive subtest. For comparison across tests on receptive and expressive language, Z scores were calculated.

Handedness measure

To assess hand preference, the Almli Handedness Assessment, Preschool Version (Almli, unpublished; see also Almli, Rivkin, & McKinstry, 2007) was administered to each participant. The Almli Handedness consists of 10 tasks performed by the participant. Each item was presented to the participant at midline and then the active hand used to complete the task was recorded (Table 1). Laterality scores were calculated as \[
\frac{\text{no. of items completed by right hand} - \text{(no. of items completed by left hand + no. of items completed by both hands})}{\sqrt{\text{total no. of items}}}\] (Michel, Ovrut, & Harkins, 1985). Laterality scores ranged from $-3.16$ (complete left-handedness) to $+3.16$ (complete right-handedness). Scores greater than $+1$ were rated as right-handed, less than $-1$ as left-handed, and scores between $+1$ and $-1$ as mixed.

Analysis

To examine group differences in age, an ANOVA was performed with group (ASD, control) as the independent variable and age as the dependent variable.

<table>
<thead>
<tr>
<th>Task</th>
<th>Active hand used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Write your name, letter, or line</td>
<td>Right</td>
</tr>
<tr>
<td>Draw a circle</td>
<td></td>
</tr>
<tr>
<td>Throw a ball to me</td>
<td></td>
</tr>
<tr>
<td>Cut paper with scissors</td>
<td></td>
</tr>
<tr>
<td>Hammer a peg in a hole</td>
<td></td>
</tr>
<tr>
<td>Use spoon to eat</td>
<td></td>
</tr>
<tr>
<td>Put piece in puzzle</td>
<td></td>
</tr>
<tr>
<td>Put lego on top of lego tower</td>
<td></td>
</tr>
<tr>
<td>Unscrew a jar</td>
<td></td>
</tr>
<tr>
<td>Put ring on rod</td>
<td></td>
</tr>
</tbody>
</table>
For language, a MANOVA was performed with group as the independent variable and receptive and expressive language $Z$ scores as dependent variables.

There may be differences in the strength of handedness, the number of right-versus non-right-handers, or both. In order to address this, an ANOVA and a chi-square were completed. To assess group differences in strength of handedness, an ANOVA was calculated with group (ASD, control) as the independent variable and Almli handedness score as the dependent variable. The handedness score was also used to classify participants as right-, mixed-, or left-handed, and a chi-square was computed to compare the groups (ASD, control) on the number of participants within each handedness category.

Pearson correlations between the handedness score and receptive and expressive language scores were computed separately for each diagnostic group. The sample was divided into right- and non-right-handers (mixed- and left-handers) to examine differences in language measures between these groups. A MANOVA was performed separately for each diagnostic group with handedness category (right, non-right) as the independent variable and receptive and expressive language scores as the dependent variables. In the ASD group, those with low language abilities were compared to those with average or above abilities on handedness measures. Receptive and expressive language was examined separately, and participants were classified as having low abilities if their score was more than 1 SD below the mean. To examine associations with language, ANOVAs were performed with receptive or expressive language group (low, average) as the independent variable and handedness score as the dependent variable.

The sample was divided into a group of younger children, 3 to 5 year olds, and older children, 6–17 years. In order to examine group differences in age, an ANOVA was run for each age group with age as the dependent variable and group (ASD, control) as the independent variable. To investigate group and age effects, an ANOVA was calculated with handedness score as the dependent variable and age group (younger, older) and diagnosis (ASD, control) as the independent variables.

**Results**

**Behavioral**

Given a violation of Levene's test for homogeneity of variances, $F(1,153) = 5.62$, $p < .02$, a Welch ANOVA was calculated. There were no significant group differences in age ($p > .05$). For language scores, Levene's test was found to be violated for receptive language, $F(1,152) = 5.34$, $p < .02$, and expressive language, $F(1,151) = 16.00$, $p < .001$, so Welch ANOVAs were used. There was a significant group effect for both receptive language, $F(2,108.21) = 88.86$, $p < .001$, and expressive language, $F(1,132.93) = 137.07$, $p < .001$, with the
control group having significantly higher language scores than the ASD group. See Table 2 for demographic and behavioral data.

**Handedness**

Given a violation of Levene's test for homogeneity of variances, $F(1,153) = 7.71$, $p = .006$, a Welch ANOVA was computed. There was a significant effect of handedness, $F(1,115.61) = 10.85$, $p = .001$; the ASD group had a significantly lower handedness score than the control group (Table 2). See Figure 1 for distribution in each group. The chi-square examining the number of right-, mixed-, and left-handers was not significant ($p > .05$; Table 3).

**Handedness-language associations**

Correlations between handedness and language measures were not significant. Table 3 presents the number of individuals in each handedness group (right, non-right) in each group. When differences in language ability were examined, in the ASD group, there was a significant handedness effect at the multivariate level.

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**Table 2.** Means and standard deviations of demographical and behavioral measures for each group. Language scores are $Z$ scores based on the language subscales of the Mullen Scales of Early Learning or the Oral and Written Language Scales. Handedness was measured with the Almli Handedness Assessment, Preschool Version, with scores ranging from $-3.16$ to $+3.16$.

<table>
<thead>
<tr>
<th></th>
<th>Autism spectrum disorder</th>
<th>Typically developing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>8.32, 3.81</td>
<td>8.57, 4.31</td>
</tr>
<tr>
<td>Receptive language</td>
<td>$-1.67$, 1.34</td>
<td>$+0.18$, 1.00</td>
</tr>
<tr>
<td>Expressive language</td>
<td>$-1.79$, 1.36</td>
<td>$+0.29$, 0.81</td>
</tr>
<tr>
<td>Handedness</td>
<td>$+1.14$, 1.88</td>
<td>$+2.02$, 1.32</td>
</tr>
</tbody>
</table>

**Table 3.** Number of individuals and percent in each group with right-, mixed-, or left-handedness based on his/her handedness score.

<table>
<thead>
<tr>
<th>Group</th>
<th>Right-handed</th>
<th>Mixed-handed</th>
<th>Left-handed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism spectrum disorder ($n = 110$)</td>
<td>74 67.3</td>
<td>16 14.5</td>
<td>20 18.2</td>
</tr>
<tr>
<td>Typically developing ($n = 45$)</td>
<td>36 80.0</td>
<td>6 13.3</td>
<td>3 6.7</td>
</tr>
</tbody>
</table>
Figure 1. The distribution of handedness scores in each group. Handedness was measured with the Almli Handedness Assessment, Preschool Version, with scores ranging from −3.16 to +3.16.
At the univariate level, this was significant for both receptive language, $F(1,106) = 4.55$, $p = .04$, $\eta^2 = .04$, and expressive language, $F(1,106) = 6.64$, $p = .01$, $\eta^2 = .06$. Both receptive and expressive language scores were higher in the right-handers relative to non-right-handers. In the control group, however, there were no significant handedness effects on language scores ($p > .05$; Figure 2).

For receptive language, 78 (71.6%) children with ASD were classified as having low language scores and 31 (28.4%) had average or above scores. There was no significant difference in handedness scores between these groups ($p > .05$; Figure 3). For expressive language, there were 80 (74.1%) children with ASD with low language scores and 28 (25.9%) with average or above average scores. There was a significant group effect, $F(1,106) = 5.23$, $p = .02$, $\eta^2 = .05$, indicating a higher handedness score in the average expressive language group than in the low language group (Figure 3).

**Age and handedness**

In the younger group (3–5 years), there were 37 children with ASD and 18 typically developing children. The older group (6–17 years) consisted of 73 children with ASD and 27 typically developing children. There were no significant
group differences in age in either age group. When handedness was examined, there was a significant effect of diagnosis, $F(1,151) = 8.43$, $p = .004$, $\eta^2 = .05$, but no significant effect of age or diagnosis by age.

**Discussion**

A handedness assessment that consisted of the direct performance of a variety of unimanual activities was used to evaluate handedness in children and adolescents with ASD compared to a typically developing control group. Scores were computed along a continuum of degree (strongly lateralized vs. less lateralized hand preference) and direction (right vs. left hand use). The sample included a large number of well-characterized children with ASD (children having completed both the ADOS and ADI, as well as other behavioral measures) with a sample size larger than most earlier studies and including two subgroups, younger children and school-aged children and adolescents. In addition, the ASD group included children with a range of language skills from above average to language impaired, which allowed examination of associations between handedness and language measures, which most prior studies have not investigated. This may help clarify the importance of differences in handedness and may identify important subgroups for development of more targeted interventions. The sample included a larger number of boys than girls; therefore, it was not possible to examine potential sex-linked differences because of limited statistical power in handedness by sex subgroups.
When strength of handedness was measured, children and adolescents with ASD had a lower mean handedness score (i.e. were less strongly right-handed) compared to the typically developing control group. This is consistent with earlier work (Cornish & McManus, 1996; Escalante-Mead et al., 2003; Hauck & Dewey, 2001; McManus et al., 1992). Hand-preference categorization was also evaluated by dividing participants into consistent right, mixed, or consistent left-handed groups. Although there was no statistical difference in the number of right-, mixed, and left-handers by group, the ASD group included slightly more combined participants with atypical hand preference (36 of 110, 33%), defined as mixed or left-handed, compared to controls (9 of 45, 20%), with a slight shift toward more left-handedness in the ASD relative to typically developing group (18.2% vs. 6.7%). This is consistent with several previous studies that showed more left-handers in the ASD group compared to controls (Cornish & McManus, 1996; Dane & Balci, 2007; Gillberg, 1983).

The relationship of hand preference to expressive and receptive language abilities was examined. As expected, standardized language scores were lower in the ASD group compared to controls. There was a significant association between language abilities and handedness in the ASD group, which was not observed in the typically developing group. As predicted, in the ASD group, a lower language score was associated with a more atypical pattern of hand preference. Both receptive and expressive language scores were higher in the consistent right-handers with ASD relative to the atypical handedness group (mixed- or left-hand preference). The effect size, however, was small, suggesting only a weak association between handedness and language ability. Few studies have examined this relationship; however, it supports Hauck and Dewey’s (2001) finding of ambiguous handedness associated with lower receptive verbal ability in young children with ASD (2–7 years), with this relationship not found in the developmentally delayed group or controls. These findings are also consistent with prior studies showing differences in asymmetry between individuals with language delay and those without. Escalante-Mead et al. (2003) found lower rates of established lateral preference (reduced degree of handedness) in adolescents and young adults with ASD with early language impairment, but no differences compared to the ASD group with normal early language acquisition. A study of children with autism and Asperger’s showed that children with language delays had left-lateralized deficits and suggested that establishment of left hemisphere dominance may differentiate those with and without language delay (Rinehart, Bradshaw, Brereton, & Tonge, 2002). Another study demonstrated anatomical differences of auditory language regions (Heschl’s gyrus, the planum temporale, supramarginal gyrus, and parietal operculum) that were more pronounced in adults with delayed language relative to those without (Floris et al., 2016). Differences in asymmetry may represent biological subgroups related to behavioral aspects of language.
Age was not a significant factor in this sample, providing support for the view that the more atypical pattern of hand preference in the ASD group may not be influenced by environmental factors that often shift people to a more consistent pattern of hand preference with increasing exposure to unimanual tool-related actions or due to a lag among children with ASD in developing an established hand preference. Some prior studies have found that hand preference in typically developing children becomes stronger and more consistently lateralized in school-aged children relative to younger children (for review, Scharoun & Bryden, 2014). Thus, longitudinal data in a large sample would be helpful to further evaluate this result.

Motor inefficiencies have been found in ASD, with school-aged children showing difficulty throwing a ball (Staples & Reid, 2010) and adults demonstrating problems in handwriting (Beversdorf et al., 2001). A recent study in adults showed fundamental differences in movement kinematics with upper limb movements more jerky and differing in velocity and acceleration relative to end-points in an ASD group compared to a control group (Cook et al., 2013). It may be that poor motor functioning results in a failure to learn the kinematic and cognitive motor skills to establish a more dominant pattern of hand preference (Bishop, 1990; Cornish & McManus, 1996). A lack of practice, due to social and communicative deficits, may also contribute to poor motor functioning and establishment of hand preference. Prior and Bradshaw (1979) did suggest that handedness in children with ASD may be the result of an inability to do the task rather than a reflection of hand preference. McManus et al. (1992) found no association between hand skill and hand preference, with many children with ASD preferring to use their less skilled hand. However, Cornish and McManus (1996) failed to replicate this result, and Hauk and Dewey (2001) showed that the more ambiguous hand preference in ASD was not due to reduced motor skills. Unfortunately, in the current study, there was no explicit examination of motor skills. Therefore, it is unclear whether a more atypical pattern of hand preference is associated with poor motor skills in children and adolescents with ASD. Direct observation of task performance showed that most participants were able to complete the items. Some participants, however, were unable to complete all of the items, particularly in the ASD group. When this occurred, these items were excluded and were not included in the calculation of the handedness score.

In the present study, brain structural or functional changes that could be associated with a more ambiguous pattern of hand preference in ASD were not examined. It is possible that areas of cortical dysfunction specific to ASD may contribute to the less consistent pattern of hand preference in the children and adolescents with ASD. Whether a more ambiguous pattern of hand preference is associated with a more bilateral cortical and subcortical disruption in these individuals requires further study (Fein, Humes, Kaplan, Lucci, & Waterhouse, 1984; Harris & Carlson, 1988). Given the association of language
skill and handedness in the ASD group, another potential biological link could
be with findings of atypical anatomical representations in frontal language zones
including the motor association portion of the inferior frontal gyrus (Joseph
et al., 2014; Knaus et al., 2009). Future research should consider whether this
pattern of atypical hand preference in ASD is associated with neuroimaging
measures of functional connectivity or with macro-structural changes in cortical
regions or in white matter pathways.

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