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Jessica Preslar April 16, 2012

Autism, lateralization, and handedness: a review of the literature and meta-analysis

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Abstract

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A number of theories of hemispheric lateralization and autism have hypothesized a link between the disorder and asymmetries in the brain. Research has been conducted to investigate this connection, but different methods and definitions have been used and the results vary widely. A systematic review and meta-analysis was conducted to assess the literature on this subject, with the hypothesis that there would be an association between autism and laterality that would be moderated by handedness, sex, age, brain region studied, and level of autism. From a broad search resulting in 259 papers, 54 were identified for inclusion in the literature review. This was narrowed further to include only studies reporting results in the inferior frontal gyrus for a meta-analysis, resulting in 4 papers. Reviewing the literature found that the majority of studies found some difference in lateralization between the autistic and control group, although what the difference was varied widely. Trends also suggested moderating variables did not have a strong influence on this relationship, although poor data quality and underrepresentation of some groups made this difficult to assess. The meta-analysis also found a moderate but non-significant effect size of group on lateralization, suggesting a decrease in the strength of lateralization in the autistic group. A subgroup analysis of sex and a meta-regression of handedness showed that these moderating variables did not have a significant effect on the relationship of autism and lateralization. Although the results are not conclusive, there appears to be a general trend towards a relationship between autism and lateralization. However, more rigorous studies with better controls and clearer reporting of definitions and results are needed.

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INTRODUCTION

The possibility of asymmetries existing in the brain has been discussed for hundreds of years, but it was not until the mid-19th century that Paul Broca and others brought the idea of lateralized function into popular scientific belief (Harrington, 1987). Currently, it is generally believed that the left and right hemispheres of the brain have differences in structure and function, although the extent and uniformity of this divergence is not entirely certain for all processes (Brancucci, Lucci, Mazzatenta, & Tommasi, 2009; McManus, 2002). One of the most consistent findings is that the majority of people have language lateralized to the left hemisphere (Dym, Burns, Freeman, & Lipton, 2011; McManus, 2002). Handedness also interacts with the lateralization of language; while approximately 95% of right handers are left brained for language, only 70% of left handers have language in the left hemisphere (McManus, 2002).

Although asymmetry has been discussed in scientific circles for over a century, several researchers have recently developed comprehensive theories to explain the causes and consequences of lateralization in the brain and in hand preference. Geschwind presented the fetal testosterone hypothesis in the 1980's, theorizing that handedness and left hemisphere development were influenced by the amount of trauma and hence testosterone in utero (Geschwind & Behan, 1982). Next, Annett postulated the existence of a 'right shift gene', which would suppress the growth of the right hemisphere and allow the left to become dominant (Annett, 1997). In her model, this gene could also undergo a mutation so that it suppressed the left hemisphere or doubly suppressed a hemisphere, leading to consequences for mental health as well as left handedness in some situations. McManus has also proposed a genetic model in which a gene coding for asymmetry can have a 'chance' allele, with certain combinations producing left handedness and a variety of mental disorders (McManus, 2002).

Autism Spectrum Disorder is a developmental disorder characterized by three general sets of features: difficulty with language and communication, reduced social functioning, and stereotyped or repetitive behaviors and interests (American Psychiatric Association., 2000). It is typically diagnosed in children, and in many cases persists through adulthood (Grinker, 2007). While not always a symptom, autism is often accompanied by reduced intelligence and mental retardation (Grinker, 2007). The medical community now recognizes autism as a spectrum disorder, with a range of functioning. One end is sometimes considered a distinct subset and is referred to as Asperger's Syndrome or High-Functioning autism. These individuals are distinguished from the main category of autism for their near-normal language skills and at or above average intelligence (American Psychiatric Association., 2000).

Past studies have found a number of neural differences between autistic and control participants. It has been suggested that there are structural, functional, and developmental differences in the brains of people with autism. Children with autism consistently have a larger total brain volume and a larger volume of the amygdala and other areas, but these are complicated by abnormal growth trajectories (Chen, Jiao, & Herskovits, 2011). A number of other regions have also reported discrepancies, including the limbic system, cerebellum, corpus callosum, and frontal and temporal lobes (Bauman & Kemper, 2005; Chen, et al., 2011; Wass, 2011). Connectivity is another feature that may differ in autism, commonly described as overconnectivity for short distances and underconnectivity for long distance tracts (Wass, 2011).

Many developmental disorders have underlying differences from control populations in asymmetry, particularly in autism (Klimkeit & Bradshaw, 2006). Data demonstrating differences in connectivity and reduced corpus callosum volume have led to the theory that unusual lateralization may contribute to the symptoms of autism. An earlier theory suggested

left hemisphere dysfunction, resulting in bilateral or rightward language (Dawson, 1983; Sussman & Lewandowski, 1990). The theory of local overconnectivity coupled with long-range underconnectivity could have implications for laterality and the connection between hemispheres. If there is less interhemispheric signaling in individuals with autism, it is possible there are also differences in lateralized organization or function. However, the link between hemispheric asymmetry and connectivity has not been firmly established (Cherbuin et al., 2012).

While there are a number of previous experiments addressing the connection between autism, handedness, and brain laterality, design flaws and different measuring techniques make it difficult to compare across studies (Philip et al., 2012). For instance, autism may not be defined specifically enough to reduce variability within each sample group and across samples. Over time, the definition of autism has changed, becoming more broad and inclusive (Grinker, 2007). This creates a problem when trying to compare across time, as well as within modern groups that may essentially have two different subsets of autism in the sample.

Another aspect to consider is handedness, since there are a number of different methods for measuring this trait. Experiments use a range of tests, including self-report, questionnaires, and behavioral testing of activities (Coren, 1993; McManus, 2002). These methods for measuring handedness can give different results; in his book on handedness, Stanley Coren notes that people report the hand used for writing when asked about their handedness (Coren, 1993). However, this may not be an accurate determination of handedness, since the preferred hand can vary between activities (Coren, 1993; Johnstone, Galin, & Herron, 1979). Further, writing is one of the activities most pressured to switch, making it a poor predictor of true handedness (Coren, 1993; McManus, 2002). After handedness has been measured, there remains the issue of coding

and interpreting the data. Handedness runs along a continuum from strongly right to strongly left handed, but researchers often find it convenient to divide people into two or three groups.

Measuring with and comparing between imaging techniques produces further issues. Within each study, researchers must make decisions about which method to use to assess asymmetry. Each imaging technique comes with its own technical concerns on how to define regions, adjust for individual differences, and compare between groups. Lateralization can be measured by a variety of structural and functional imaging techniques, testing subjects at rest or performing a specified task. Also, when measuring, there are two distinct aspects of laterality which are not always clearly differentiated: strength and direction. Strength refers to the amount of asymmetry, or how different the two sides are, while direction refers to whether the left or right side is stronger. These two interacting features of asymmetry, as well as individual variation, contribute to difficulties in studying lateralization. Possibly due to the variation between studies, they often report conflicting results on the association between autism and lateralization.

Together, this variation in methods and outcomes suggests a comprehensive systematic review is necessary to combine outcomes between studies. A meta-analysis will allow for the quantitative assessment of possible moderator variables and the average effect size of autism on strength of lateralization. In addition, a thorough qualitative review of the literature is necessary to provide additional information on the interaction of autism and asymmetry and possible moderators.

To address some of these problems and integrate information, a systematic literature review was performed to explore the association of laterality and handedness in an autistic and control group. Specifically, it was hypothesized that there would be a difference in brain

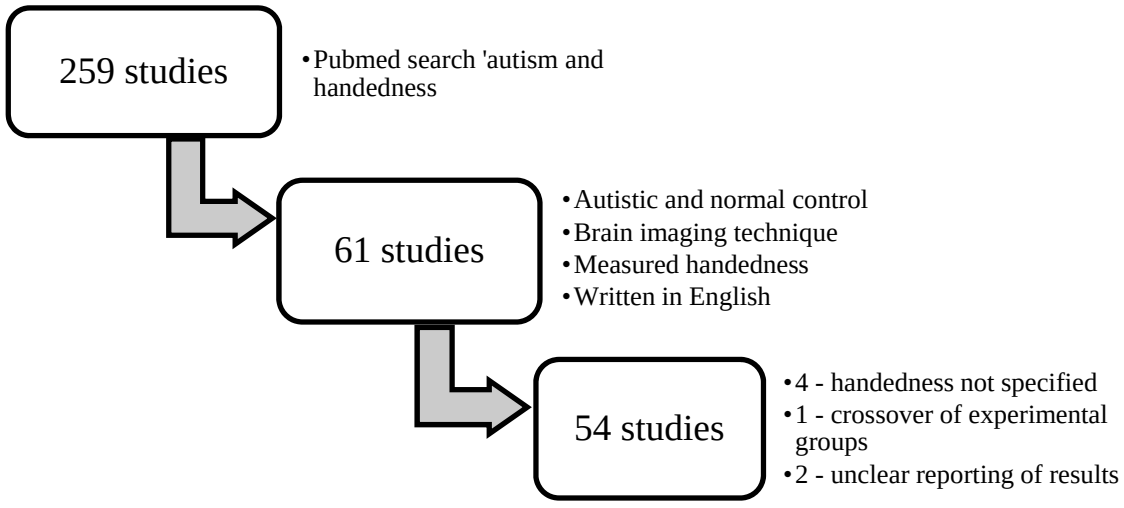
lateralization between autistic and control groups as measured by imaging techniques, and that this difference in asymmetry would be correlated with a difference in handedness. Other moderator variables of the effect of autism on brain laterality were hypothesized to be sex, age, brain region studied, and level of autism.

Methods

Data Sources

Studies were identified for inclusion through an online search in the Pubmed database (see Figure 1).

Figure 1: Study selection



The keywords ‘autism’ and ‘handedness’ were used to produce a large range of results, totaling 259 papers. Abstracts and papers were inspected to identify which studies met the inclusion criteria. To be considered for inclusion, studies had to measure handedness and some form of laterality in the brain using an imaging technique in an autistic group and a control group. This allowed the relationship between neural asymmetry and handedness to be examined

directly with minimal participant variation, as well as keeping the number of studies at a reasonable level. Studies were included that measured handedness and that controlled for it as a confounding variable. To qualify as measuring brain laterality, a structural or functional brain imaging technique was necessary, including magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), magnetoencephalography (MEG), and others. Using one of these methods, the experiment had to measure lateralization or hemispheric interaction by comparing left and right brain areas or interhemispheric connectivity. These factors had to be measured in a normal control group, not another group of clinical or disabled individuals. If the study had multiple experimental groups, such as a group of autistic and a group of dyslexic individuals, only the autistic group was compared to the normal control group and included in the sample size *n*. The last criterion for inclusion was that the study must have been written in, or translated to, English.

Studies could also be discarded for a number of reasons. Exclusion criteria included not measuring a specific function of the brain directly, such as using visual sacchades to measure asymmetry. Applying these broad inclusion and exclusion criteria yielded 61 studies. After in-depth examination of the papers, 4 more were excluded for not specifying the handedness of the participants, despite controlling for it as a variable. In one case, two experiments conducted by the same researcher a year apart clearly examined the same group (same number, age range, and IQ range), so the more recent study was eliminated. Two more studies were discarded for reporting results in an unclear manner; one did not distinguish results between autistic and language impaired groups, and the other used ‘ipsilateral’ or ‘contralateral’ to discuss the results

rather than ‘right’ or ‘left’. When all of these criteria were considered, it resulted in a final number of 54 studies[1].

Variables

A complete list of the variables recorded and categories within each is presented in Appendix A. Most variables were extracted directly from the studies. Age range, how autism measured, sex, how handedness measured, handedness results, type of brain measurement, how brain asymmetry measured, and number of participants were all variables simply reported by the studies and easy to extract, usually needing no recoding or interpretation. In the ‘trying to measure’ variable, a study was counted as having its primary aim to measure laterality if asymmetry, laterality, or differences between hemispheres were mentioned in the stated purpose or hypotheses. ‘Level of autism’ was likewise based on the report of the study, on if the researchers limited the group to high-functioning individuals or had a mix representing the full spectrum. If the authors did not specify the level of autism, occasionally verbal IQ scores were used to help decide whether a group was exclusively high-functioning; however, a conservative approach was taken, so that indirect measures could only rule out an exclusively high-functioning level, it could not put them in that category. The variables determining if sex and

[1] (Alexander et al., 2007; Anderson et al., 2011; Ashwin, Baron-Cohen, Wheelwright, O'Riordan, & Bullmore, 2007; Belmonte & Yurgelun-Todd, 2003; Burnette et al., 2011; Cheon et al., 2011; Chiron et al., 1995; Conturo et al., 2008; Dawson, Finley, Phillips, & Galpert, 1986; Dawson, Finley, Phillips, & Lewy, 1989; Flagg, Cardy, Roberts, & Roberts, 2005; Fletcher et al., 2010; Freitag et al., 2008; Gaffrey et al., 2007; Gomot, Giard, Adrien, Barthelemy, & Bruneau, 2002; Greimel et al., 2010; Harris et al., 2006; Herbert et al., 2002; Hodge et al., 2010; Jou et al., 2011; Jou, Minshew, Keshavan, Vitale, & Hardan, 2010; Kasai et al., 2005; Ke et al., 2009; Keary et al., 2009; Kleinhans, Muller, Cohen, & Courchesne, 2008; Knaus et al., 2010; Knaus, Silver, Lindgren, Hadjikhani, & Tager-Flusberg, 2008; Kosaka et al., 2010; Koshino et al., 2005; Kumar et al., 2010; Lange et al., 2010; Lazarev, Pontes, & deAzevedo, 2009; Lazarev, Pontes, Mitrofanov, & deAzevedo, 2010; Lo et al., 2011; Martineau, Cochin, Magne, & Barthelemy, 2008; Martineau, Schmitz, Assaiante, Blanc, & Barthelemy, 2004; Mason, Williams, Kana, Minshew, & Just, 2008; Minagawa-Kawai et al., 2009; Mizuno et al., 2011; Mizuno, Villalobos, Davies, Dahl, & Muller, 2006; Muller, Kleinhans, Kemmotsu, Pierce, & Courchesne, 2003; Noriuchi et al., 2010; Oades, Walker, Geffen, & Stern, 1988; Rojas, Camou, Reite, & Rogers, 2005; Samson et al., 2011; Scheel et al., 2011; Schmidt, Rey, Oram Cardy, & Roberts, 2009; Schmitz et al., 2006; Schmitz et al., 2008; Schultz et al., 2000; Turner, Frost, Linsenbardt, McIlroy, & Muller, 2006; Wallace, Dankner, Kenworthy, Giedd, & Martin, 2010; Whitehouse & Bishop, 2008; Wilson, Rojas, Reite, Teale, & Rogers, 2007)

handedness were controlled were also based on what was reported by the authors. The 'other' variable was a widely-defined variable, simply noting if there was a confounding factor mentioned by the authors but not controlled for in the study or analysis. Examples typically included a large difference between groups in medication profile or in method of sedation for scan that could create systematic differences in results.

'Brain regions studied' were often listed as individual regions of interest; however, due to their large number and diversity, they were combined into broad functional regions based on stated purpose for analysis. This produced larger groups and allowed a focus on cohesive functions rather than individual areas. It also facilitated comparison between studies. The broad region into which a study was classified depended on what the authors identified as their primary region of study. The papers typically contained a discussion of the areas to be studies and what type of function they performed. If it was not explicitly stated in the paper, the broad region was sometimes obvious based on specific regions examined; for example, pars opercularis and triangularis are well-known components of the language system (Newman, Just, Keller, Roth, & Carpenter, 2003). However, if it was not clear, the study was coded as multiple or other for this variable. Further, if the whole brain was measured but differences were only found in and listed by specific regions rather than averaged across the whole brain, it was grouped by the region the differences were found in, since that is the area on which the difference in lateralization variable will also be based. A sample of the specific regions of interest examined by studies that fall into each category is listed in Appendix B. These regions were compared to ensure there was some overlap between areas that authors defined as being in a particular region, even if they were not identical in every study.

Outcome variables were specified as any difference in lateralization, relative asymmetry for autistic and control groups, and what difference in lateralization exists, and they were more complex variables that sometimes required interpretation from the text. 'Any difference in lateralization' was the simplest and most basic outcome, a dichotomous yes/no variable recording if the study found any difference in lateralization, asymmetry, or interhemispheric connectivity between groups. No distinction was made between studies measuring averaged hemispheric asymmetry and asymmetry of specific regions, since there was not a clear way to combine and compare across these differences.

Relative asymmetry findings were recorded for the autistic and control group, and then used to determine what the difference in lateralization was when the information was readily available and easy to interpret. The author's reported results or tables were used to determine these differences in asymmetry. The 'what difference in lateralization' compares the relative asymmetries of the autistic group versus the control group, and it shows what the difference in laterality or interhemispheric connectivity was. This variable was recorded to attempt to determine some of the underlying subtleties in the difference in lateralization; however, it was not always easily discernible from the results reported. Particularly if the results were reported by comparing each hemisphere between groups without comparing them within groups, it was clear there was a difference in direction of lateralization but the difference in strength was unclear. For example, if a study reported a difference in the left hemisphere but not the right hemisphere, it was clear there was some difference in asymmetry; however, without knowing how the left and right hemisphere were related in the control group, it was impossible to determine how the asymmetry relationship differed between groups. A trend in the direction of laterality could be assessed, but nothing about the strength of laterality could be inferred. Again,

these were approximate and categorical variables, and were not examined for all studies due to a lack of easily discernible information regarding the relative levels of activation or structural measures in the left and right hemisphere of autistic and control groups.

As previously discussed, the lateralization variables were determined in studies that measured a specific region or overall hemispheric asymmetry and connectivity. While nonspecific, this is a broad approach that allows for any difference in lateralization to be counted. Likewise, if a study measured several different areas and found differences in some but not others, it was counted as having a difference in lateralization between groups. It should also be kept in mind that a difference in lateralization is different from a difference in extent of function. Many studies found a difference in activation, but if they found the difference bilaterally then there would be no difference in asymmetry.

Handedness results were constructed variables based on the proportion of non-right handers reported in each group in most cases. For this analysis, non-right handed was defined as left handed or ambidextrous. It was not possible to standardize the definition of non-right handedness based on a single cut-off point for each test, since most papers did not give the cut-off number used. Additionally, the studies operated under the assumption that they were defining and often controlling for handedness, so it might lead to a different interpretation of the results to come back after comparisons have been made and change the definition. Studies were defined as controlling for handedness included those that used all right-handed participants as well as those that had a mix of right and left-handed individuals, as long as there was no difference between the autistic and control groups

Difference in handedness was assessed in most studies individually using a chi-square test of independence or Fisher's exact value. The chi-square value and significance level were

recorded, as well as phi as a measure of effect size. To compare the three studies that did not report frequencies to the majority, a student's t-test was used to generate a p-value for the difference between means.

To explore the relationship between handedness and laterality, a new dichotomous variable was first created to divide studies based on handedness. Since only two studies showed a statistically significant chi-squared value, effect size in the form of phi was used. A broad approach was used similar to the difference in laterality variable; studies were classified into those that had no effect size of handedness and those that had a non-zero phi. No minimum cut-off of effect size was used, since most were low. In this way, the variable of any difference in handedness essentially divides studies into those in which handedness could play a role and those in which handedness almost certainly has no effect.

The variable of 'any difference in handedness' was examined in three ways. First, it was compared to the variable of 'any difference in laterality' to see how many studies matched on these two measures (showed a difference or did not show a difference for both variables) and did not match (showed a difference in only one variable). Studies were also divided by the variable of 'any difference in handedness', and the outcome of 'any difference in laterality' was compared between these two groups. Finally, the dichotomous variable of 'handedness controlled' was used to split studies, and lateralization was again compared between these two subgroups of studies.

Originally, IQ differences and how the sample was recruited were also going to be moderator variables. However, after examining these data in several studies, it became clear that they are not reported often enough to yield any meaningful data.

Statistical Analysis

The data was imported into the IBM SPSS software for analysis. Descriptive statistics such as frequencies were assessed and presented in the systematic review below. Sorting methods were used to find differences in the frequency of the outcome variable within different subgroups.

For the purposes of a meta-analysis, a smaller subgroup of the studies used for the literature review was chosen to increase the comparability and to allow a meaningful and logical interpretation of the results. Since studies looked at a diverse collection of brain regions, it would be difficult and have questionable meaning due to the heterogeneity of the aims and form of results reported to compare across all of them (Lipsey & Wilson, 2001). Instead, the inferior frontal gyrus (IFG), containing Broca's area, was chosen as a region with well-studied laterality in normal subjects that is also highly applicable to autism spectrum disorder (Nunez et al., 2011; Stefanatos & Baron, 2011; Yamasaki et al., 2010). Previous studies and systematic reviews have found differences between control and autistic subjects in the inferior frontal gyrus (Tesink et al., 2011; Via, Radua, Cardoner, Happe, & Mataix-Cols, 2011).

Of the 54 studies, 19 were identified as measuring and reporting data from the IFG or a sub-region, including pars opercularis, pars triangularis, lateral frontal area, or Broca's area. For data to be accepted as amendable to an effect size calculation, mean and standard deviation or t-value had to be reported for a lateralization index in the IFG. Out of the 19 studies identified, 15 did not report data in a suitable manner to be included, primarily because they did not report a lateralization index. A lateralization index is a standardized measure of the difference between the two hemispheres, typically calculated as a percent difference. This resulted in 4 studies for

which effect size of group on strength of lateralization index in the inferior frontal gyrus or sub-regions could be calculated. A summary of these studies is presented below in Table 1.

Effect sizes were used to compare across studies, as is the typical course for a meta-analysis suggested by a number of books on the subject (Michael Borenstein, 2009; Hedges & Olkin, 1985; Hunter & Schmidt, 1990; Lipsey & Wilson, 2001) and used in several recent meta-analyses (Murphy et al., 2012; Via, et al., 2011). Since most studies reported the dependent variable as a continuous measure but used different metrics, a standardized difference of means was chosen as the effect size (Michael Borenstein, 2009; Lipsey & Wilson, 2001). Hedge's g was used as a correction for small sample size to produce an unbiased estimate of true effect size, since in small studies the traditional difference of means tends to overestimate (Michael Borenstein, 2009; Hedges & Olkin, 1985). Effect sizes were calculated by hand from one of two sets of data regarding an index of lateralization provided by the study: mean, standard deviation, and sample size; or t-test value and sample size. Since it is not always possible to distinguish between direction and strength of laterality when averaging, the absolute value of the lateralization index was used to examine the strength of asymmetry. The direction of laterality observed in each study is presented qualitatively in Table 1 below. All equations for calculating effect size and variance were from books by Borenstein and Lipsey (Michael Borenstein, 2009; Lipsey & Wilson, 2001).

To compare across effect sizes, a trial version of the software Comprehensive Meta-Analysis was used (M Borenstein, Hedges, Higgins, & Rothstein, 2005). For each of the four studies, Hedge's g and variance were entered into the program. A summary effect size was calculated, and a forest plot generated (see Figure 2). A random effects model was chosen for the combination of effect sizes across studies, since there is no justification for believing the

studies share a true effect size. As Borenstein and colleagues point out, there are very few situations in which a fixed-effects model is appropriate, and the variability of participant characteristics certainly precludes the assumptions for a fixed effect model in this meta-analysis (Michael Borenstein, 2009). This decision was supported by the results of a test for homogeneity, with a significant result and therefore a rejection of the null hypothesis that differences between studies were due to chance ($Q=12.159$, $df=3$, $p=.007$).

Since publication bias has been shown to be a pervasive problem in research, Duval and Tweedie's Trim and Fill method was used to attempt to quantify the impact of this bias (Michael Borenstein, 2009; Hedges & Olkin, 1985). This method was chosen due to concerns about the applicability of other methods, including basic funnel plots and Rosenthal's fail-safe N, to small numbers of studies, as well as their validity in general (Michael Borenstein, 2009; Hedges & Olkin, 1985; Lipsey & Wilson, 2001).

Finally, to test the additional hypothesis of an interaction between handedness and laterality in autism and to assess the impact of other moderator variables, a meta-regression and a subgroup analysis were performed. Handedness was coded by the effect size phi, and compared against laterality effect size using a method of moments meta-regression, again based on a random effects model.

Subgroup analysis was used to assess categorical variables. Originally, the moderators desired were age, level of autism, sex, and type of imaging technique. The information for each of these variables, as well as handedness, for the studies included is displayed in Table 1. As the table makes apparent, only sex could be analyzed using subgroup analysis, since age, level of autism, and type of imaging technique did not have adequate information to produce any meaningful results. Consistent with the overall analysis, a random effects model was adopted

since sex cannot be assumed to account for all of the variation between studies. A pooled T^2 estimate of between studies variance was used, as Borenstein and colleagues suggest a subgroup estimate based on few studies may be less precise than pooling across all subgroups (Michael Borenstein, 2009).

Results

Literature Review

All studies had a quasi-experimental study design, with participants non-randomly assigned to group based on diagnostic condition. Researchers made attempts to different degrees to match participants between groups on other characteristics.

The studies range in time from 1986-2011, with over half written after 2007. The total number of participants across all 54 studies was 884 in the autistic group and 864 in the control group, with an average of 16.4 autistic and 16.0 control participants per study. Although all of the experiments measured laterality in some form, only 26 (48.1%) named measuring laterality or asymmetry as a primary objective of the study. Others concentrated on finding a diagnostic measurement for autism or were examining differences in the autistic brain that they recorded by left and right hemisphere.

The participant population in each study was varied. The most common age range studied was children and adolescents (18/54, 33.3%), followed closely by adolescents and adults (13, 24.1%), adults (9, 16.7%), children (7, 13.0%), all three groups (5, 9.3%), and adolescents (2, 3.7%). Overall, half (27/54) looked exclusively at children and adolescents. Slightly over half (31, 57.4%) of the studies looked exclusively at males, while most of the rest had males and females in their groups (22, 40.7%). One study did not specify the sex composition of the

groups, only stating that they were matched. Most of the studies used groups that were matched for sex by having the same number of females in each group (47, 87.0%). A slight majority of studies (31, 57.4%) also controlled for handedness. For the autistic group, 23 (42.6%) studies were limited to high-functioning forms of autism, while 17 (31.5%) used a mix of autistic individuals from different levels of the spectrum. However, 25.9% did not specify what level of autism was included in the experimental group.

A variety of methods were used to gather data on autism, handedness, and laterality. Almost all studies used multiple methods to define autism (49, 90.7%), including ADI-R, ADOS, and DSM/ICD criteria. The other 5 studies used only one of these or other measures (9.3%). The most common method reported for measuring handedness data was the Edinburgh Handedness Inventory (13, 24.1%). However, a relatively high percentage (20, 37.0%) did not mention any method for collecting handedness data. If it is assumed handedness was assessed in these experiments through self-report, then this method would represent the highest frequency, with a total of 24 (44.4%) studies. Asymmetry and interhemispheric connectivity were measured using a large variety of imaging techniques. fMRI was the most common (17, 31.5%), followed by DTI (9, 16.7%), MRI (8, 14.8%), EEG (6, 11.1%), and MEG (4, 7.4%). Four experiments employed multiple methods of brain imaging (7.5%), and 6 used other methods (11.2%).

The brain regions studied in each experiment were spread out over a range of areas. Language areas and whole cortex were the most common foci, with 10 studies each (18.5% each). Six (11.1%) studies primarily examined social areas, while 5 (9.3%) studies looked at each of perception areas and frontal areas. Nine experiments examined and found differences in multiple regions (16.7%), and 5 studies looked at multiple white matter tracts (9.3%). Three other papers studied unclassified regions (5.6%), primarily the corpus callosum.

Seven studies (13%) were found to have significant, unexplained and unaccounted for confounding variables such as medications or systematic differences between groups in methodology, while 47 (87%) did not have any obvious confounds that could produce systematic differences. However, many studies had missing methodology data, possibly indicating poor study quality.

Across all studies, 44 (81.5%) found some difference in laterality between an autistic and a control group, while 10 (18.5%) found no difference. Of the 36 for which more information was readily available, 10 found no difference in lateralization between groups, and 9 found decreased laterality in the autistic group. Five reported increased laterality in the autistic group, 4 with the increase towards the left hemisphere and 1 with an increase towards the right. Eight studies demonstrated an approximately equal strength of laterality but a reversal of direction. For studies measuring interhemispheric connectivity through the corpus callosum, 4 found a decrease in connectivity in the autistic group while none found an increase. The high number of studies in this subgroup that found no difference in lateralization most likely reflects the relative ease to extract this information from a study compared to determining the strength and direction of a difference in lateralization.

Studies were further divided by aim, level of autism, and brain region to examine the outcome of laterality within different categories. Of the 26 studies with a primary goal of studying laterality, 23 (88.5%) found a difference in lateralization; in contrast, 75% (21/28) of studies not specifically looking at laterality found such a difference. When divided by level of autism, 13 of the 17 (76.5%) of the studies that included a mixed group of autistic individuals found a difference in laterality. This is slightly lower than the 87% (20/23) of studies exclusively using high-function autism that found a difference in asymmetry. For brain regions,

the proportion of studies that found a difference in laterality was roughly similar across regions (90% in language areas, 80% in perception areas, 66.7% in social areas, 80% in frontal areas, 80% in multiple white matter tracts, 77.8% in studies looking at multiple areas, and 90% in those looking at the whole cortex). In each group there were also relatively small numbers of studies, so these percentages generally reflect a difference of one or two studies.

The effect size of group on handedness, measured by phi, ranged from -.397 to .430, with an average of .038. As described above, these data were coded into a dichotomous variable; 32 studies (59.3%) had an effect size of 0, often because handedness was controlled, while 19 (35.2%) had a non-zero value of phi. It was found that 23 (42.6%) of studies found that differences in laterality and handedness agreed, while 28 (51.9%) reported a difference in just one variable. This most likely reflects the large number of studies that controlled for handedness and then found a difference in laterality.

Next, the results of laterality were split based on whether the study found any difference in handedness. Within the 32 studies in which the effect size of group on handedness was zero, 7 (21.9%) found no difference in lateralization. In contrast, only 3 (15.8%) of the 19 studies with some effect size on handedness reported no difference in lateralization. This is consistent with the idea that handedness and lateralization are connected, although there might be a relationship between autism and laterality even when handedness is constant (shown by the 25 studies that found a difference in laterality with no difference in handedness). This also highlights that the 28 studies reporting a disagreement between handedness and laterality results is driven by studies that controlled for handedness (25 had no difference in handedness), while the 3 that found no difference in laterality could have had very low, insignificant effect sizes of handedness.

An alternative approach is to assess laterality in studies that did and did not control for handedness. The outcome of laterality was again assessed separately in studies that did and did not control for handedness. This should and in fact does produce similar results to the analysis based on any difference in handedness, since the researchers' intentions to control for handedness should result in no difference of handedness. Of the 31 studies in which handedness was intentionally controlled, 8 (25.8%) found no difference in lateralization. When handedness was not controlled, only 2 of the 23 studies (8.7%) found no difference in asymmetry.

Meta-analysis

Study and participant characteristics of the four studies included in the meta-analysis are depicted in Table 1 below (Burnette, et al., 2011; Chiron, et al., 1995; Herbert, et al., 2002; Knaus, et al., 2008). The combined number of participants across studies was 81 autistic and 65 control individuals.

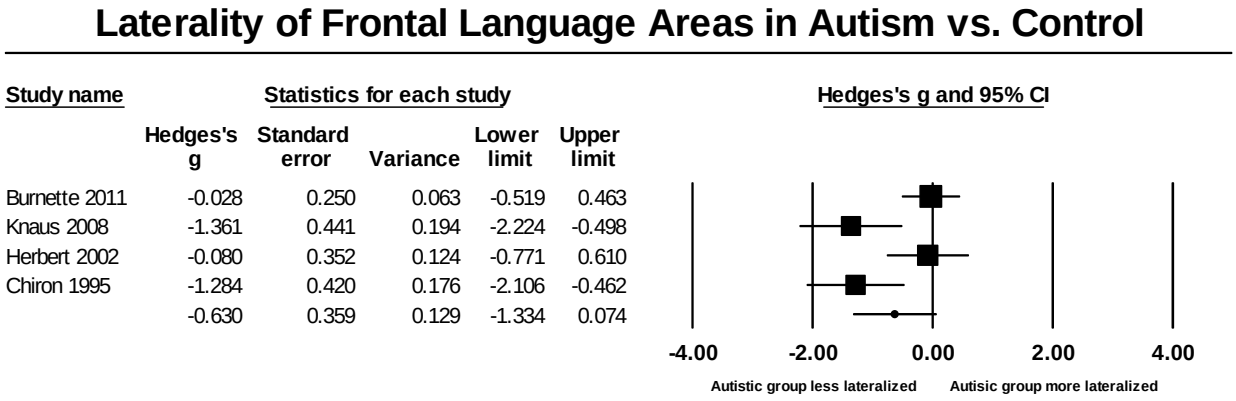
Table 1: Study characteristics

	Age Range	Level of Autism	Sex	Handedness Controlled	How handedness measured	Effect size of group on handedness	How lateralization measured	Task used during measurement
Burnette, 2011	Children	HFA	Mixed	Yes	-	0	EEG	At rest
Knaus, 2008	Adolescent	Mixed	All Male	Yes	Self-report; modified Dean	0	fMRI	Semantic word-production
Herbert, 2002	Children	-	All Male	Yes	-	-.271	MRI	(Structural)
Chiron, 1995	Children and Adolescent	-	Mixed	No	Dellatolas questionnaire	.430	SPECT	At rest

	Pertinent areas examined	How data reported	Qualitative results, direction of laterality	Hedge's g	Variance of g	Autistic sample size	Control sample size
Burnette, 2011	Lateral frontal area	Mean and SD of LI for each group	RH>LH in both groups	-0.0283	0.0627	35	28
Knaus, 2008	Pars opercularis, pars triangularis	Mean and SD of LI for each group	LH>RH in both groups	-1.361	.1941	12	12
Herbert, 2002	Pars opercularis, pars triangularis	Mean and SD of LI for each group	LH>RH control; RH>LH autistic	-0.0804	.1242	16	15
Chiron, 1995	Broca's area	t-value for comparison of LI between groups	LH>RH control; RH>LH autistic	-1.284	.1761	18	10

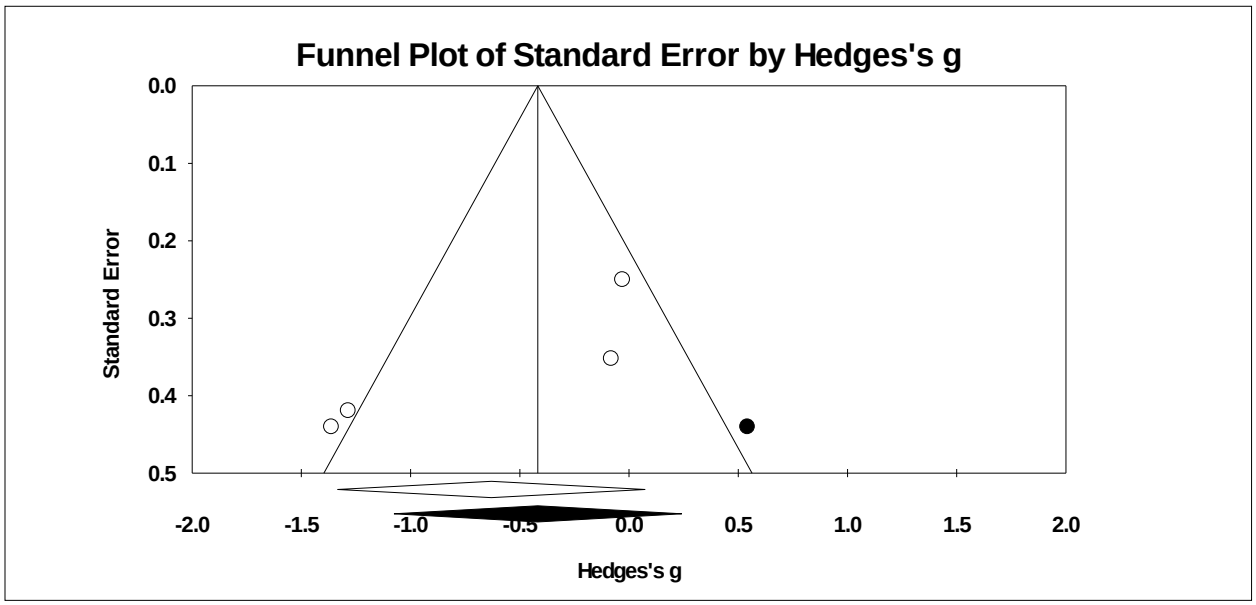
Based on the random effects model, the mean effect size given in terms of Hedge's g was moderate but not significant (g= -0.630, p=0.079, SE=0.359, 95% CI= -1.334, 0.074). As demonstrated by the p-value and the confidence interval, the null hypothesis cannot be rejected with significance level set at alpha=.05. Figure 2 shows the forest plot, with the effect size of each study and the summary effect on the bottom row. The value of T^2, which estimates the variance between effect sizes of the population of studies, was 0.382 (Michael Borenstein, 2009).

Figure 2: Summary Effect Size



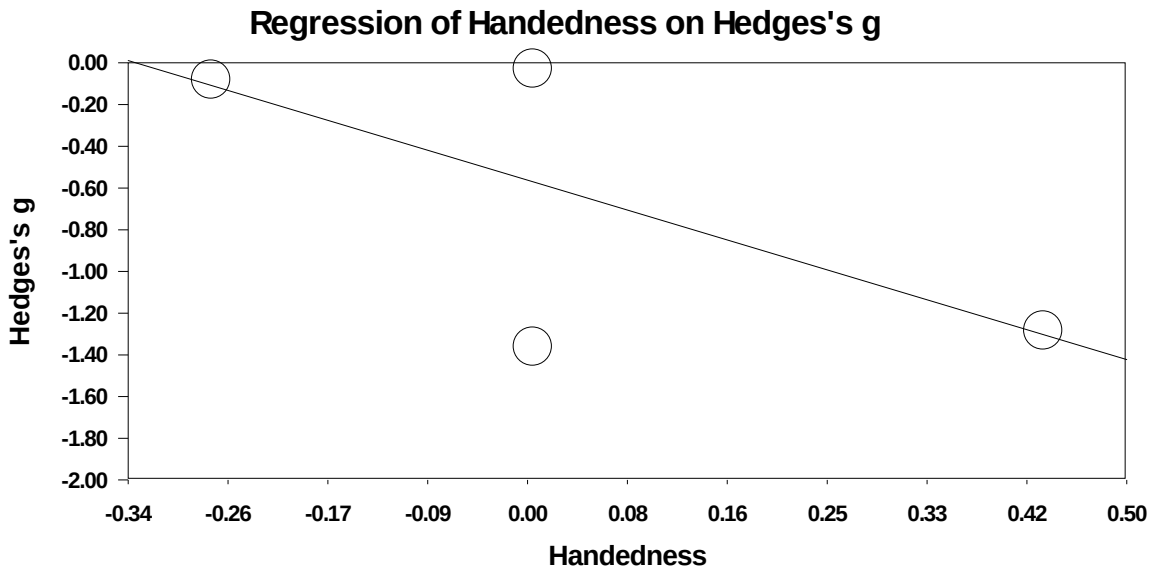
Duval and Tweedie's trim and fill method to correct for publication bias resulted in a corrected, presumed unbiased, effect size of g= -0.417 (95% CI= -1.076, 0.2412) based on the random effects model, with an adjusted Q value of 16.519. As Figure 3 shows, one imputed value was added closer to the null value to approximate the presumed missing small study with a low or absent effect size, making the funnel more symmetric around the mean.

Figure 3: Publication Bias



The meta-regression of laterality and handedness revealed a slope of -1.705, p=.205, SE = 1.344 (95% CI -4.340, .929) for the method of moments (see Figure 4). This non-significant result implies that there was not a relationship between laterality and handedness in these studies, although this could have been influenced by the very small number of studies.

Figure 4: Meta-regression of handedness



The subgroup analysis of sex revealed that there was no difference in effect size of studies that used only males and those that included both. Using a random effects analysis with pooled T^2, the average effect size of studies using males was -.694 and for studies including both males and females was -.611. The total between studies Q value was .009, p=.926. This suggests that there was no difference in effect sizes based on using exclusively males or a mixed group. However, the low number of studies gives a low statistical power, and the extremely low number of females typically included in studies containing both could have resulted in the groups appearing similar.

Discussion

The literature review reveals the variability within the design and findings of studies on laterality and autism, while also suggesting a trend towards a difference in lateralization for the autistic group. Although there is a huge variety of results, it appears that the majority found

decreased, reversed, or no difference in lateralization. Differences between study characteristics, including the region studied and the task they used during the experiment, most likely interacted with other moderator variables to produce this large range of results.

Dividing the studies into subgroups for the literature review based on potential moderator variables produced no clear trends; in fact, contrary to expectations, the data looked remarkably similar for any difference in lateralization and the type of difference when separated by aim, level of autism, and brain region studied. This could be because the differences across groups are too subtle to be detected by categorical variables. For example, high-functioning and mixed groups of autistic individuals could have brain laterality decrease compared to controls by different amounts, a subtlety that would not be picked up by the literature review. Another possible explanation is that none of these moderator variables has any effect on the lateralization of the brain between autistic and control groups, although this goes against previous knowledge about the variability in the autistic spectrum and in the laterality of different brain regions in normal populations. Instead, the huge variability across results suggests that a more probable possibility is that there is simply too much variation in the studies themselves to allow for accurate interpretation of results.

The results of the difference in handedness between groups did not appear to match previous findings of increased numbers of non-right handedness in autistic populations. Although many studies controlled for handedness, and therefore the results cannot be compared with frequencies from randomized trials, only two tests had significant p-values for the chi-square or t-test. However, the studies had very small sample sizes and often did not report how they measured handedness.

The interaction of handedness and laterality appears slightly stronger, when laterality outcomes were assessed in terms of handedness by group. When the asymmetry variable was divided into subgroups by 0 or non-zero effect size or in terms of controlled/not controlled for handedness, those that found a difference in handedness or where it was not controlled were more likely to show a difference in lateralization. This matches previous literature on handedness and laterality, and it demonstrates that not properly controlling for handedness may introduce a confounding variable to the study. However, there may be a more subtle relationship between the two measures of laterality. Currently, handedness measures are reported primarily by the direction, which may be less related to a decrease in lateralization than the strength of handedness. To measure this, validated questionnaires or behavioral tests must be used and analyzed as a continuous variable rather than grouping into a dichotomous or categorical variable. Again, however, the results must be interpreted cautiously due to variability within the outcomes of the studies.

The literature review offers no conclusive results about differences in laterality, but simply points to the necessity for further investigation and highlights interesting trends. The majority of studies did find some difference in laterality, suggesting that the association between this variable and autism needs to be studied more. However, this collection of studies was not uniform, so no precise conclusions about which aspects of laterality or which specific regions are most associated with autism can be assumed. Further, simply counting the number of studies that find significant results can generate a misleading representation of the data (Michael Borenstein, 2009; Hedges & Olkin, 1985).

The results of the meta-analysis support the trend from the literature review of a decreased magnitude of lateralization in the autistic group. The averaged effect size was

moderate, but only trended towards significance. As the Figure 2 shows, the combined estimate of effect size had large confidence intervals due to large within and between studies variance in the random effects model. More studies would be needed to draw any definitive conclusions on the size of the effect of autism on brain laterality.

The subgroup analysis and meta-regression were used to assess the association between laterality and a moderator variable between groups. There was no effect of sex on the relationship between autism and asymmetry; in fact, the effect sizes were almost identical between these two groups. The meta-regression was also non-significant, but the trend was towards an association between an increase in the difference of handedness and laterality between groups. Although it is based on a very small number of studies, it might be of interest to note that this seems to only hold true for an increase in non-right handers in the control group; in the study with more non-right handers in the autistic group, the effect size for group on lateralization was close to zero. This could potentially imply that there may be a difference in the degree of lateralization between left-handed autistic and control samples. However, without more studies or a more consistent effect size, the data can only suggest trends and highlight the need for further investigation.

Taken together, the literature review and meta-analysis suggest that there is a difference in the degree of laterality between autistic and control samples, and that it cannot be entirely explained by a difference in the direction of handedness. However, the trend towards a decrease in laterality could help explain differences in handedness observed in the past.

These results fit into all of the main theories of lateralization and handedness, since it suggests a relationship between the developmental disorder of autism and the strength of asymmetry in the brain. Without further knowledge of the way in which laterality was

decreased, either across the whole hemisphere or only in specific regions, it would be difficult to determine which theory was most supported by these data.

Another potential explanation for the difference between autistic and control subjects on lateralization and handedness comes from the idea that culture is partially responsible for the predominance of the right hand. If culture indeed influences some people to become more right handed than they would have been otherwise, this social pressure may simply not produce a strong response or not be directed at autistic individuals. As previous studies have shown, autistic children have decreased gaze direction understanding and are less able to learn a task from watching others (Nadel et al., 2011; Pellicano & Macrae, 2009). If this was the case, it could make them less strongly right handed, and possibly not as strongly lateralized as a result of less practice with the right hand.

One of the problems raised by the question of autism and lateralization is the difficulty of studying lateralized function in hand preference or in the brain. Lateralization of hand preference and cerebral functions is measured on a continuum, with two characteristics that are not always distinguished. Laterality can be defined in terms of direction and strength, and one does not necessarily say anything about the other. Because of the way they are situated along a continuum, averaging across conditions can lead to confusing results. For example, Dawson and colleagues point out that although the average activation by hemisphere in their groups suggests the autistic group has roughly symmetric activation, this is in fact due to some autistic individuals being lateralized to the right and some to the left (Dawson, 1989). This could also be applicable on the individual level; for handedness and hemispheric asymmetry, averaging across multiple measures or functions/regions would produce identical results for an individual who was highly lateralized but mixed for direction and someone who had weak lateralization. Some

studies avoid this problem by further dividing participants based on direction of lateralization and then comparing groups. However, this can make it more difficult to interpret the results and directly answer a question about laterality with them.

Handedness can also be difficult to measure and interpret. However, while there is no single way of measuring handedness always used, previous research has demonstrated some methods to be more correlated with brain lateralization (Johnstone, et al., 1979). Johnstone, et al. found in an early study that questionnaires had a higher correlation with brain lateralization based on EEG and dichotomous listening tests than skill measures or self-report. Further, there was a much clearer association between handedness and lateralization when a continuous measure was used for handedness rather than dividing participants in categorical groups (Johnstone, et al., 1979). Still, the majority of studies used self-report as the only method of determining handedness.

Primary studies had several other limitations in addition to the measurement of laterality and handedness. Overall, the studies were very concentrated on specific functional regions of the brain or specific questions, without trying to relate findings to other functions or overall lateralization. A variety of tasks were used, giving more information on neurological correlates for behavioral measures but less helpful for comparing across studies. Another prevalent factor was the variability in interpretation of differences in activation, suggesting that a standard is necessary for relating functional activation to skill. Also, if studies are using handedness to try to control for individual atypical lateralization, they must record and report handedness in greater detail to address the strength as well as direction of manual lateralization. In any case, this might not be an adequate standard. More research needs to investigate typical lateralization of handedness, language, and other functions and the interactions between these variables.

One main limitation of the primary studies involved variation, within and between studies. Within studies, many did not match groups properly on extraneous variables, such as IQ, medications, and method of recruitment. Further, several studies had missing information that they either failed to record or report. There are also problems related to imaging studies, particularly when dealing with large individual variability (Belmonte, 2003). Some investigators did attempt to address this issue by using methods that allow for more individual variation rather than blurring and averaging across groups (Belmonte, 2003). Between groups, missing information and a broad range of methods for performing the experiment and reporting data made it difficult to compare across groups. This large variation is exacerbated by small sample sizes, leading to low power for analysis.

Activation, and by extension asymmetry, is interpreted in different ways between authors or between tasks. In some studies, authors concluded that an increase in activation resulted because the participants were better at a task; in others, the authors claimed that subjects with more activation were in fact less skilled at the task, and therefore had to recruit more areas. Presumably these conclusions were in part founded on behavioral measures as well and not simply imaging studies. However, it highlights the problem in task-prompted functional studies of comparing the same thing across groups. Researchers must make the assumption that there are not systematic differences in the way the groups approach the task or which regions they recruit. A difference in activation could reflect the autistic group using a different neural process for a task rather than a difference in lateralization for one function.

Several studies also had confounding variables, most notably the presence of medications or other comorbid disorders in the autistic but not the control group. Thirteen percent of studies had some type of confounding factor that was not accounted for or controlled for in the

experiment. In a number of studies, multiple autistic subjects were on one or more medications. These medications could have potential effects on brain activation measures and perhaps on laterality, since activation of some neurotransmitter systems has been shown to be lateralized (Martin-Soelch et al., 2011). Other conditions that are often comorbid with autism, including lower IQ and anxiety disorders, could affect brain imaging results (Belmonte & Yurgelun-Todd, 2003). Laterality may be related to differences in intelligence as measured by IQ tests, so it is difficult to discern the distinct effects of autism and IQ on laterality (Mercure et al., 2009).

Another factor that was often unaddressed was the dearth of information on females with autism. Studies often excluded females to increase the homogeneity of groups. However, this leads to less than half of the studies including any females. Even when participants were not exclusively male, the proportion of females was almost always lower than the 20% generally reported in the autistic population (Volkmar, Szatmari, & Sparrow, 1993). Previous studies have suggested that lateralization differs between the sexes, so the relationship of this variable to laterality in autism needs to be examined more thoroughly (Johnstone, et al., 1979; Wada et al., 1996).

For handedness, studies using questionnaires should make sure their method is valid for testing the direction and magnitude of asymmetry. Once this is measured, it must be reported as an average rather than as a number left/right. Researchers automatically make it a less precise variable by reducing it to a dichotomous question, as well as mask potential differences in magnitude of lateralization within the individual (Johnstone, et al., 1979).

In the combination of primary studies, further limitations apply to the meta-analysis and its interpretation. A huge limitation in data analysis and interpretation of the results is the heterogeneity of studies gathered. While intended to give a broad perspective on the question

and integrate several sources, it makes the studies less comparable and the results more difficult to meaningfully combine. As the test for homogeneity shows, even the effect sizes for the meta-analysis subset differ significantly from one another. Also, studies often measured and reported results for a large number of areas in the brain, each essentially a dependent variable for which an effect size would have to be calculated or which would have to be combined. When studies take several measures then only report the statistically significant ones, it can also create a type of within-study publication bias (Hedges & Olkin, 1985).

Using the researchers' categories can be problematic and contribute to this heterogeneity, as they are usually not clearly defined and might differ between studies. Particularly in the 'brain region studied' category, there was some variation between what areas were actually measured by the researchers (see Appendix B). Defining regions by function could also be problematic or inaccurate, since there can be individual variation in brain structure or function (Ecker et al., 2012). Researchers often included different regions of interest in their studies, covering a broad range of potential functions. However, given the information available, it was not possible to define categories and redistribute studies according to one standard. This again highlights the necessity of using standardized definitions across studies and including a clear discussion in the paper of standards used.

Changing definitions of autism over the time span of the group of studies could also lead to heterogeneity and make it more difficult to compare outcomes. Since 1986, when the first study included was published, the diagnosis of autism has become more inclusive and a larger number of cases have been reported (Fombonne, 2003; Grinker, 2007). This could create a systematic bias in the samples included from early versus late studies, particularly if what is now called high-functioning autism is indeed a distinct disorder from low-functioning autism.

Separating studies based on high versus mixed autism revealed no difference in outcome; however, the mixed groups could include an increasing number of high-functioning individuals as the diagnosis becomes more common. A heterogeneous diagnostic group could introduce an additional confounding factor that cannot be accounted for by this meta-analysis.

As noted previously, the dichotomous variable of 'difference in laterality' was broadly defined and may therefore not mean the same thing for every study. It represented if there was a significant difference between groups for the relationship of left hemisphere to right hemisphere; in other words, if there was an interaction between the group and the laterality variables. However, studies were looking at different aspects of laterality and interhemispheric connectivity, including measures of activation and structure on the left and the right, divided by region and averaged across the hemisphere, as well as the corpus callosum. There were many studies that produced some mixed results, such as differences in one area between hemispheres and groups but not in others. This was considered justified since the purpose of this systematic review was to examine all of the knowledge to date regarding brain laterality, handedness, and autism from imaging studies. By taking a broad, inclusive stance, the question of if any difference in laterality or interhemispheric connectivity is supported by evidence could be addressed over a range of methods and approaches. This also prevented a biased exclusion of studies from certain time periods, since methods of imaging and trends in research on laterality and autism have changed. However, it also clearly points to the need for further investigation, both at the primary study level and meta-analytic level.

In addition to limitations of the current literature review, the practice in general of counting frequencies of studies may be less rigorous than desired. The method of examining the frequencies of studies that found significant results, sometimes called vote-counting, has been

called into question by several authors (Michael Borenstein, 2009; Hedges & Olkin, 1985). They claim that using statistical significance unnecessarily divides studies into a dichotomous variable and may count studies as having no effect if they simply have a low sample size. However, others take more moderate approaches, suggesting that p-values can yield some useful information if the data needed to calculate effect sizes cannot be readily obtained (Hartung). In light of these objections, the frequencies presented in the literature review should be interpreted cautiously, as mentioned previously.

Particularly for the meta-analytic portion, the typical assumption is that all studies included have the same null hypothesis, even if they use different measures to test it (Lipsey & Wilson, 2001). While not all of the studies included here had the stated goal of testing laterality, all took measurements in a way that contributed something to the knowledge about asymmetry. This was typically done through presenting data for each region by hemisphere. Therefore, although the aims were not uniform, the outcomes had some relevance to laterality. The meta-analysis and subgroup and regression analyses also included only four studies, a low number from which to try to draw conclusions. Particularly with the meta-regression, Borenstein highlights the problems with using this method for low study numbers (Michael Borenstein, 2009).

Although ideally the problem of too few studies in the meta-analysis could have been corrected by simply adding more studies, it was sometimes difficult to determine a single effect size that measured lateralization exactly. Even when a study reported the data necessary to calculate effect size, it could be difficult to create one outcome since a large number of 'regions of interest' were typically outlined and measured. This essentially created dozens of dependent variables with separate means and variances. One would first have to select a specific region to

study (as in the current analysis) or somehow combine all regions to look at the overall hemisphere. When averaging across the whole hemisphere, you would lose information on whether functions are lateralized to the left and the right or simply weakly lateralized. Additionally, each experiment may not measure or report every region of the brain, so even a 'whole hemisphere' measure could differ between studies. For example, many studies only report the p-values for significant results, in effect creating a type of publication bias within the study. Alternatively, with the raw data, a meta-analyst could go all the way down to the voxel level to combine and compare subjects. And this does not take into account types of brain imaging besides fMRI and MRI, like DTI or MEG, which give results in an entirely different way. With these limitations of averaging across the whole hemisphere, the approach of choosing a single region was chosen, despite its own shortcomings.

In future studies, researchers must consider hypotheses in relation to the study of laterality, handedness, and autism in order to standardize definitions and produce comparable results. They should be particularly sensitive to reporting their data in a manner amenable to the study of asymmetry, most easily achieved by calculating a lateralization index from the raw data.

Future studies should also address issues presented above, including issues related to handedness, lack of female participants, variability within autism, IQ, and population recruitment. These variables must be standardized within and across studies, and they must be presented in a clear manner. Ideally, a research team would examine handedness and hemispheric asymmetry, both divided by regions and averaged across the hemisphere, in a large number of control, high-functioning autistic, and low-functioning autistic participants who were properly matched.

Additionally, a deeper, more thorough meta-analytic approach needs to be taken. Effect sizes should be calculated to estimate the strength of the relationship between autism and laterality of different areas of the brain and to give a more nuanced answer to the question. While it may be impossible to compare across all studies looking at handedness and brain laterality in an autistic sample, studies could be divided into groups based on region and subdivided into functional and structural differences to be analyzed. Although a more fragmented view, this method might provide a more realistic and accurate picture of differences in the brains of people with autism that may underlie their condition. These results could then be assessed as a group to see if any trends emerge.

If laterality is associated with autism, it has implications for future diagnosis and possibly treatments in addition to research. While the field of brain imaging is far from providing reliable diagnostic tools for most developmental disorders, any connection between the experienced mental state and the underlying neurobiology may enhance the ability of caretakers to identify, understand, and treat the disorder. The simple knowledge that a relationship might exist between autism and asymmetry of the brain can prompt more specific and targeted research in the field.

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Appendix A: Variables

Variable	Codes/Categories
Trying to measure	0 – Primary aim to measure lateralization 1 – Lateralization not stated as a primary aim
Age range	0 – Children (<13 yrs) 1 – Children and adolescents (<18 yrs) 2 – Adolescents (13-18 yrs) 3 – Adolescents and adults (13+ yrs) 4 – Adults (19+ yrs) 5 – Children, adolescents, and adults (any age)
Level of autism	0 – Mix/spectrum 1 – High functioning or Asperger's Syndrome
How autism measured	1 – Single measure 3 – Multiple measures
Sex	0 – Male 1 – Male and female
Sex controlled	0 – Groups matched on sex 1 – Groups not matched on sex
Handedness controlled	0 – Handedness controlled 1 – Handedness not controlled
How handedness measured	0 – Edinburgh handedness inventory 1 – Annett handedness scale 2 – Observation 3 – Self-report 4 – Lateral dominance examination 5 – Multiple 6 – Neurological examination/questionnaire
Handedness results, autism group	Number non-right handed (continuous)
Handedness results, control group	Number non-right handed (continuous)
Handedness between groups	Chi-square or t-test value (continuous) p-value for chi-square or t-test (continuous) Phi, effect size (continuous)
General difference in handedness	0 – Phi = 0 1 – Phi is not 0
Type of brain asymmetry measured	0 – Asymmetry/lateralization 1 – Hemispheric connectivity 2 – Both
How brain asymmetry measured	0 – MRI 1 – fMRI 2 – DTI 3 – MEG 4 – EEG 5 – Multiple
Brain region studied	0 – Language areas

	1 – Perception areas 2 – Social areas 3 – Frontal areas 4 – Multiple white matter tracts 5 – Multiple regions 6 – Whole cortex 7 – Cerebellum
General difference in asymmetry	0 – No difference 1 – Yes, is difference
General findings, autism group	0 – LH=RH 1 – LH>RH 2 – LH<RH
General findings, control group	0 – LH=RH 1 – LH>RH 2 – LH<RH
What difference in asymmetry	0 – No difference 1 – Decreased laterality 2 – Increased laterality towards left 3 – Increased laterality towards right 4 – Equal but reversed laterality 5 – Decreased hemispheric connectivity 6 – Increased hemispheric connectivity
Lateralization and handedness	0 – General laterality and handedness agreed (were both different or both the same) 1 – General laterality and handedness different results
Number participants	Number in autistic group (continuous) Number in control group (continuous) Total number in study (continuous)
Other confounding variable	0 – No confounding variables/conditions 1 – Obvious confounding variables/conditions

*For all variables, 9998 = other; 9999 = missing (both coded as missing)

Appendix B: Brain Regions

Region Label	**Sample of Brain Areas Included**
Language areas	Superior temporal gyrus; temporal stem; arcuate fasciculous; planum temporale; inferior frontal gyrus; pars opercularis; pars triangularis; frontal and temporal language areas
Perception areas	Auditory cortex; Heschl's gyrus; occipital areas; posterior temporal regions; central and parietal areas;
Social areas	Superior temporal sulcus; cuneus; anterior cingulate cortex; dorsolateral prefrontal cortex; amygdala; superior longitudinal fasciculous; superior temporal gyrus
Frontal areas	Mid-frontal areas; laterlal frontal areas; middle frontal gyrus; medial frontal gyrus; language gyrus; cuneus
Multiple white matter tracts	Anterior and posterior thalamic radiations; uncinate fasciculous; cingulum; arcuate fasciculous; corpus callosum; fronto-occipital fasciculous