

Social Cognition and Brain Morphology: Implications for Developmental Brain Dysfunction

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Published online: 2 May 2014
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Abstract The social-cognitive deficits associated with several neurodevelopmental and neuropsychiatric disorders have been linked to structural and functional brain anomalies. Given the recent appreciation for quantitative approaches to behavior, in this study we examined the brain-behavior links in social cognition in healthy young adults from a quantitative approach. Twenty-two participants were administered quantitative measures of social cognition, including the social responsiveness scale (SRS), the empathizing questionnaire (EQ) and the systemizing questionnaire (SQ). Participants underwent a structural, 3-T magnetic resonance imaging (MRI) procedure that yielded both volumetric (voxel count) and asymmetry indices. Model fitting with backward elimination revealed that a combination of cortical, limbic and striatal regions accounted for significant variance in social behavior and cognitive styles that are typically associated with neurodevelopmental and neuropsychiatric disorders. Specifically, as caudate and amygdala volumes deviate from the typical R>L asymmetry, and cortical gray matter becomes more R>L asymmetrical, overall SRS and Emotion Recognition scores increase. Social Avoidance was explained by a combination of cortical gray matter, pallidum (rightward

asymmetry) and caudate (deviation from rightward asymmetry). Rightward asymmetry of the pallidum was the sole predictor of Interpersonal Relationships and Repetitive Mannerisms. Increased D-scores on the EQ-SQ, an indication of greater systemizing relative to empathizing, was also explained by deviation from the typical R>L asymmetry of the caudate.

These findings extend the brain-behavior links observed in neurodevelopmental disorders to the normal distribution of traits in a healthy sample.

Keywords MRI · Brain morphology · Autism spectrum disorder · Social cognition · Quantitative traits

Introduction

Successful social interactions rely on a host of adaptive traits that enable individuals to understand the thoughts, feelings, intentions and behaviors of others (Skuse and Gallagher 2011). These skills may involve pragmatic language ability, empathy, social perspective-taking, inferring inner states of others, and making social attributions based on social cues, among others. Many neurodevelopmental disorders (ND) – particularly autism spectrum disorders (ASD) – are defined, in part, by deficits in social behavior (Couture et al. 2010). These social behaviors are well characterized and have been tied to a number of developmental genetic, neural, environmental and evolutionary influences.

Recent years have witnessed an important shift in the ways that we regard neurodevelopmental and neuropsychiatric (NP) disorders. We use the term Developmental Brain Dysfunction (Moreno-De-Luca et al. 2013) to describe the overlap among neurodevelopmental (NDD) and neuropsychiatric (NPD) disorders that have traditionally been viewed as separate and distinct clinical entities. In addition to the common behavioral

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phenotypes shared across many DBDs, there is also growing evidence that such disorders share common neural, genetic and molecular mechanisms (Cristiano et al. 2014; Moreno-De-Luca et al. 2013; Stefansson et al. 2014). The overlap among clinical syndromes is supported by a quantitative approach to behavioral phenotyping, which is contrast to the traditional “normal-abnormal” taxonomic approaches that have long dominated the fields of clinical psychiatry and psychology. The quantitative approach also regards psychological and behavioral “symptoms” as extreme ends of normally-distributed traits that are represented in the general population (Constantino 2011; Moreno-De-Luca et al. 2013). In this study, we take a quantitative approach to examining the structural, neural substrates of a set of normally distributed behaviors—social responsiveness, social cognition, empathy and repetitive mannerisms – that are implicated in a wide range of disorders characterized by developmental brain dysfunction (Moreno-De-Luca et al. 2013).

Many of the behaviors associated with DBDs such as autism spectrum disorders (e.g. deficits in perspective-taking and social reciprocity, restricted interests and repetitive behaviors), are observed in close relatives of children with ASD, including those who do not meet the threshold for clinical diagnosis of ASD (Baron-Cohen et al. 1997; Baron-Cohen et al. 2007; Baron-Cohen et al. 1998; Baron-Cohen et al. 1997; Constantino et al. 2010; Losh et al. 2008; Virkud et al. 2009). Indeed many, if not all, behavioral traits that define the phenotype of ND and NP disorders have normative variants in the general population. Epidemiologic studies have shown that quantifiable traits that make up the core impairments of ASD (such as those measured with the Social Responsiveness Scale (SRS)), are continuously distributed in the general population (Constantino and Todd 2003; Ronald et al. 2006). Other features associated with ASD that also appear in the general population include repetitive behaviors and restricted interests (Baron-Cohen and Wheelwright 1999; Evans et al. 1997; Pietrefesa and Evans 2007), deficits in theory of mind, and a systemizing (as opposed to empathizing) cognitive style (Baron-Cohen et al. 2003; Baron-Cohen and Wheelwright 2004).

Systemizing refers to a way of interacting with others, and the world more generally that reflects rule-based systems, such as mechanical, natural, abstract, or collectible systems. Systemizing is highly characteristic of persons with ASD. In the context of typical functioning, systemizers represent the end of a spectrum in terms of pursuit of activities and occupations that reflect the areas of science, technology, engineering, and mathematics. On the other end of the spectrum are empathizers whose interaction styles rely on understanding the internal states of others and socialized perspective-taking (Baron-Cohen et al. 2003; Baron-Cohen and Wheelwright 2004).

Given measures with sufficient sensitivity to capture the normal distribution of the social and behavioral traits

associated with ASD – such as systemizing – important information may be gleaned in terms of common brain-behavior links that underlie both normal and pathological behavior. Standard diagnostic measures of ASD (such as the Autism Diagnostic Observation Schedule, or ADOS) reflect the traditional categorical approach to symptom expression. While these clinical measures serve as important tools for identifying ASD case status, they yield near floor-effects in non-clinical populations thus masking important brain-behavior links that may underlie the typical manifestations of ASD behaviors.

The social deficits, restricted interests and repetitive behaviors observed in many DBDs have been linked to a range of neural structures including limbic, cortical-striatal circuitry, and cortical gray matter volume. In ASD, common findings include: enlarged cerebellum relative to controls (Hardan et al. 2001; Minshew and Williams 2007); enlarged amygdalae (Abell et al. 1999; Groen et al. 2010; Howard et al. 2000; Juranek et al. 2006; Munson et al. 2006; Murphy et al. 2012; Schumann et al. 2004; Sparks et al. 2002), enlarged caudate (Hollander et al. 2005; Langen et al. 2007; Sears et al. 1999) and enlarged hippocampal volume (Groen et al. 2010; Rojas et al. 2004, 2006; Schumann et al. 2004; Sparks et al. 2002; see also Amaral et al. 2008 for a review; c.f. Saitoh et al. 2001 reporting reduced dentata volume in ASD).

Considerable evidence also points to the importance of hemispheric (a) symmetry in typical and atypical populations. Typical populations generally exhibit rightward asymmetry ($R > L$) of several structures including cortical gray matter, the amygdala and hippocampus (Filipek et al. 1994; Geschwind and Galaburda 1985; Oertel-Knochel et al. 2012; Pedraza et al. 2004; Toga and Thompson 2003; Visser et al. 2013). Deviations from this typical asymmetry may be indicative of underlying pathology (Wang et al. 2001; Weiss et al. 2005; Woodward et al. 2011), and greater symmetry in the amygdalae and hippocampi has been observed in ASD, schizophrenia, and bipolar disorder (Blumberg et al. 2003; Hier et al. 1979; Oertel-Knochel et al. 2012; Oertel-Knöchel and Linden 2011). Indeed deviations from normal symmetry patterns are considered by some to be a useful endophenotypic marker for DBD (Sharma et al. 1999; Woodward et al. 2011).

Studies comparing clinical disorders to healthy controls are important for understanding the underlying neural functions that may give rise to atypical behavior. But such studies also introduce artificial dichotomies between “normal” and “pathologic” neural and behavioral functioning, possibly obscuring the proposed continuity between typical and atypical brain-behavior links. The quantitative approach is not limited to behavioral measures, but rather extends to neural traits and the expression of genetic traits as well.

Healthy individuals who are higher in empathy relative to systemizing ($E > S$) exhibit differential functional brain activity during a judgment task relative to $S > E$ subjects (Focquaert et al. 2010). In males, $S > E$ is positively correlated with

occipital white matter integrity, but this correlation is negative in female participants (Chou et al. 2011). $S > E$ is also associated with greater white matter volume in the cingulum and the dorsomedial prefrontal cortex (Lai et al. 2012a, 2012b). These findings are consistent with work noting gray matter/white matter anomalies in brain regions involved in social cognition and other behaviors associated with ASD (McAlonan et al. 2005; Minshew and Williams 2007; Verhoeven et al. 2010; Via et al. 2011), especially limbic, frontal and striatal brain regions.

Aside from these studies, we know very little about the shared variance between quantitative ASD traits and brain structures in healthy subjects. In this study, we explore the shared variance between quantitative traits associated with ASD and other disorders, and neural structures that may govern these traits. We believe that such efforts will help us understand the brain-behavior links that underlie both typical and atypical social behavior, and will provide avenues for future research.

Methods

The research protocol and consent procedures were approved by the Institutional Review Boards of Bucknell University (IRB#1112-033, “Social Cognition and Face Perception”) and Geisinger Medical Center (IRB# 2012–0329, “Social Cognition and Functional Brain Imaging: Extending the Autism Phenotype”). All subjects involved in the study gave written informed consent.

Statistical analysis

All analyses were performed using SPSS 20 (IBM) with a significance threshold of $p < 0.05$. Variable distributions were checked for normality and we determined that there was no need to run non-parametric analyses based on the lack of assumption violations in parametric tests.

Participants

Subjects were undergraduate students at a university in central Pennsylvania (N=24; 12 male, 12 female). Subjects were recruited through an introductory psychology course for satisfaction of optional partial research credit and monetary compensation for completion of the entire study. All subjects had normal to corrected-normal vision. One participant was removed from the analysis based on left-handedness and another was removed due to taking medication for a psychiatric diagnosis. This left a total of 22 (10 female) participants, with no psychiatric diagnoses based on self-report, for statistical analysis.

The average age of the remaining participants was 19.10 (SD=1.07) years. Nineteen of the participants were Caucasian, while there was one participant each of African American, East Asian, and South Asian descent.

Behavioral and Demographic Measures

Participants were administered an online battery of inventories including demographics, the Social Responsiveness Scale, the Empathizing Quotient and the Systemizing Quotient-revised. These online measures were administered through Qualtrics (<http://www.qualtrics.com/>) survey software.

Subjects were asked to complete an online demographics form with information on gender, race, date of birth, ethnicity, religion, psychiatric history, familial psychiatric history, and parental behaviors.

(SRS-A) (Constantino and Todd 2005; Constantino et al. 2003). The SRS-A is a 65-item self-report measure of ASD traits. Each item is measured on a 4-point (0–3) scale. The SRS has been studied extensively as a valid and reliable quantitative measure of ASD-related behaviors, and has normal skewness and kurtosis. Recent confirmatory factor analysis indicates that the best fit is a 5-factor model. These factors are: Emotion Recognition, Social Avoidance, Interpersonal Relatedness, Insistence on Sameness, and Repetitive Mannerisms. This version of the SRS was normed for ages 19 years and over. However given that the participants were all at least 18.5 years of age, this version was used for all subjects (see Table 1 for means and standard errors, by sex).

(EQ and SQ-R) (Simon Baron-Cohen and Wheelwright 2004; Wheelwright et al. 2006). The EQ is a 40-item self-report measure of empathy. The SQ-R is a 75-item self-report measure assessing systemizing tendencies. Both are rated on a 4-point scale, “definitely agree”, “slightly agree”, “slightly disagree”, and “definitely disagree.” A D-score (difference) is derived by first standardizing each participant’s raw EQ score ($E = \frac{EQ - (\text{mean } EQ)}{80}$) and raw SQ-R Score ($S = \frac{SQ - (\text{mean } SQ)}{150}$). The difference between these two standardized scores results in a D-score, $D = \frac{S - E}{2}$. Negative D-scores reflect relatively more empathizing trait expression, whereas positive D-scores reflect relatively more systemizing traits (Lai et al. 2012a, 2012b).

MRI Data collection

Magnetic resonance imaging was performed with a GE Discovery MR750 3 T scanner (GE Medical Systems) with a standard 32-channel RF head coil at Geisinger Medical Center, Danville, PA. High contrast three-dimensional T1-weighted structural images were acquired at a resolution of

Table 1 Means and Standard Errors on Measures of Social Behavior for Males and Females

Measures of Social Cognition	Mean \pm SEM		F	Sig. (<i>p</i>)
	Male	Female		
SRS Scales				
Total score	46.22 \pm 12.78	46.29 \pm 17.20	0.00	0.99
Emotion recognition	16.60 \pm 5.75	20.84 \pm 6.05	2.83	0.11
Social avoidance	5.77 \pm 2.79	5.79 \pm 3.79	0.00	0.99
Interpersonal rel.	3.25 \pm 2.80	3.30 \pm 2.58	0.00	0.97
Insistence on sameness	13.81 \pm 4.83	12.30 \pm 5.63	0.46	0.51
Repetitive mannerisms	6.79 \pm 3.67	4.06 \pm 2.51	3.98	0.06
EQ-SQ				
D-Score	0.02 \pm 0.03	-0.06 \pm 0.03	3.46	0.08

0.938 \times 0.938 \times 1.2 mm. This high-resolution structural scan was taken as part of an extended protocol and was also used for anatomical co-registration of functional data.

Volumetric analysis

NeuroQuant[®] software was used to analyze and report volumetric data. NeuroQuant[®] provides fully automated segmentations that have been validated against manual methods and has obtained 510 K approval by the US Food and Drug Administration as a device for providing quantitative segmental volumes (Brewer 2009; Kovacevic et al. 2009). The procedure used by the software utilizes three-dimensional T1-weighted MRI images to register brain anatomy to a probabilistic atlas for anatomical labeling. Specific cortical and sub-cortical volumes were calculated – including absolute volume (cm³) and corrected for intracranial volume (ICV) – as well as an asymmetry index included the forebrain parenchyma, cortical gray matter, lateral ventricles, inferior lateral ventricles, hippocampi, amygdalae, caudate, putamen, pallidum, thalamus, and cerebellum. These regions have emerged in previous research as candidate sites implicated in the pathogenesis of ASD. ICV corrected volumes are presented as a percentage of overall ICV. The asymmetry index is defined as the differences between left and right structure volumes divided by their mean – in percent. A positive asymmetry index indicates greater left-versus-right asymmetry while a negative indicates greater right-versus-left asymmetry.

Results

Brain region asymmetry and brain region volumes and their differential relationships to social cognition were examined using manual model fitting with backwards elimination through a series of multiple regression analyses. Multiple regressions were performed separately to determine the role

of a) brain structure and regional volumes (corrected for intracranial volume, or ICV) on social cognition and b) asymmetry indices on social cognition, by examining the following structures: cortical gray matter, lateral ventricles, hippocampus, amygdala, caudate, putamen, pallidum, and cerebellum. As mentioned above, these regions have previously been identified to vary in volume in ASD populations (hippocampus, amygdala, cerebellum, and cortical gray matter: Sparks et al. 2002; Aylward et al. 1999) or to play a role, via the prevalence of oxytocin receptors, in social cognitive abilities (corpus striatum: Ross & Young, 2009; Young, Lim, Gingrich, & Insel, 2001). Thus, these regions are strong candidates for volumetric and hemispheric analyses associated with social cognition.

First, to determine potential sex differences between brain regions and measures of social cognition, a series of One-Way ANOVA tests were conducted (See Tables 1 and 2). Using ICV-corrected brain volumes, some initial volumetric and lateralization differences were noted but these did not remain significant after Bonferroni correction (corrected $p=0.006$). Therefore, males and females were combined for subsequent analyses. Participant age was not correlated with any of the measures of social behavior or gray matter volume/asymmetry (all p -values >0.05).

We note striking consistency across our results indicating that volumetric and asymmetry indices of brain regions that are implicated in ASD predict various measures of social cognition.

Multiple regression analysis examined brain region volumes and regional asymmetries as predictors of total SRS-A scores as well as each of the five subscales (see Tables 3 and 4). After manual model fitting with backwards elimination (we employed the standard threshold of $p>0.2$ to remove coefficients not contributing to the model) several regional brain asymmetries explained variance in the SRS-A total score. Forty-two percent of the variance in the SRS-A score was explained by three regional asymmetry indices (Adjusted

Table 2 Volumetric and Asymmetry Comparisons of Males and Females

Brain region volume (% of ICV)	Mean±SEM		F	Sig. (<i>p</i>)
	Male	Female		
Cortical gray matter	34.81±1.01	36.77±0.46	2.73	0.11
Lateral ventricle	0.95±0.10	1.14±0.13	1.33	0.26
Hippocampus	0.47±0.01	0.51±0.01	6.01	0.02*
Amygdala	0.21±0.01	0.21±0.00	0.21	0.65
Caudate	0.43±0.02	0.46±0.03	0.75	0.40
Putamen	0.66±0.02	0.71±0.01	3.22	0.09
Pallidum	0.13±0.00	0.13±0.00	0.23	0.64
Cerebellum	1.11±0.03	1.60±0.45	1.45	0.24
Asymmetry indices	Mean ± SEM		F	Sig. (<i>p</i>)
	Male	Female		
Cortical gray Matter	-1.10±0.35	-1.64±0.37	1.15	0.30
Lateral ventricle	24.16±28.93	-0.66±7.79	0.58	0.46
Hippocampus	-1.53±1.49	-7.32±1.46	7.54	0.01*
Amygdala	-3.37±1.66	-0.14±2.79	1.07	0.31
Caudate	-3.17±4.98	-4.64±4.72	0.05	0.83
Putamen	6.66±2.67	4.25±1.77	0.52	0.48
Pallidum	-7.48±6.53	3.94±3.17	2.17	0.16
Cerebellum	1.10±0.49	2.79±0.52	5.59	0.03*

Table 3 Brain Region Asymmetry Predicting Social Responsiveness and D-Score

Measure	F	Adj. R ²	Brain region	B (SE)	β	t (<i>p</i>)
SRS-A total score	4.75**	0.42	Cortical gray matter	-5.20 (2.23)	-0.42	-2.33 (0.03)*
			Amygdala	1.01 (0.35)	0.50	2.84 (0.01)*
			Caudate	0.57 (0.18)	0.61	3.10 (0.01)**
			Pallidum	-0.319 (0.16)	-0.41	-2.00 (0.06)
SRS-A emotion recognition	9.53***	0.55	Cortical gray matter	-1.93 (0.78)	-0.37	-2.47 (0.02)*
			Amygdala	0.48 (0.13)	0.57	3.73 (0.002)**
			Caudate	0.16 (0.06)	0.41	2.76 (0.01)*
SRS-A social avoidance	2.93*	0.31	Cortical gray matter	-1.20	-0.44	-2.25 (0.04)*
			Hippocampus	-0.19	-0.33	-1.71 (0.11)
			Caudate	0.11	0.56	2.58 (0.02)*
			Pallidum	-0.10	-0.61	-2.68 (0.02)*
			Amygdala	0.12	0.28	1.46 (0.16)
SRS-A interpersonal relationships	2.64	0.19	Cortical gray matter	-0.91 (0.46)	-0.41	-1.99 (0.06)
			Hippocampus	-0.17 (0.10)	-0.36	-1.71 (0.10)
			Pallidum	-0.07 (0.03)	-0.49	-2.25 (0.04)
SRS-A Insistence on sameness	No significant predictors					
SRS-A Repetitive mannerisms	3.25	0.18	Caudate	0.08 (0.05)	0.39	1.76 (0.10)
			Pallidum	-0.10 (0.04)	-0.54	-2.43 (0.03)*
D-Score	7.06*	0.22	Caudate	0.003 (0.001)	0.51	2.66 (0.02)*

Table 4 Brain Region Volumes Predicting Social Responsiveness and EQ-SQ D-Score

Measure	F	Adj. R ²	Brain region	B (SE)	β	t (p)
SRS-A total score	3.35	0.18	Lateral Ventricle	-15.51 (7.59)	-0.41	-2.05 (0.06)
			Pallidum	-373.84 (192.80)	-0.39	-1.94 (0.07)
SRS-A Emotion recognition	No Significant Predictors					
SRS-A social avoidance	5.59*	0.18	Cortical gray matter	-0.52 (0.22)	-0.47	-2.36 (0.03)*
SRS-A Interpersonal relationships	2.53	0.18	Lateral ventricle	-2.93 (1.42)	-0.43	-2.06 (0.05)
			Amygdala	39.23 (27.94)	0.31	1.40 (0.18)
			Pallidum	-89.14 (38.71)	-0.51	-2.30 (0.03)*
			Hippocampus	-46.86 (14.19)	-0.56	-3.30 (0.004)***
SRS-A Insistence on sameness	No significant predictors					
SRS-A Repetitive mannerisms	13.45***	0.54	Cortical Gray Matter	-0.37 (0.20)	-0.32	-1.86 (0.08)
			Cerebellum	0.06 (0.03)	0.39	1.91 (0.07)

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

$R^2 = 0.42$, $p < 0.01$). Higher SRS-A scores were significantly related to increasing leftward (L>R) asymmetry of the amygdala (standardized $\beta = 0.50$, $p < 0.05$), increasing leftward asymmetry of the caudate ($\beta = 0.62$, $p < 0.01$), and increasing rightward asymmetry (R>L) of overall cortical gray matter ($\beta = -0.42$, $p < 0.05$) (See Fig. 1).

Backward elimination regressions were also performed on calculated D-Scores. Symmetry indices yielded a significant model but regional volumes did not. Rightward asymmetry of the caudate was significantly related to an increasing D-Score (more systemizing cognitive style) (Adjusted $R^2 = 0.22$, $\beta = 0.51$, $p < 0.05$).

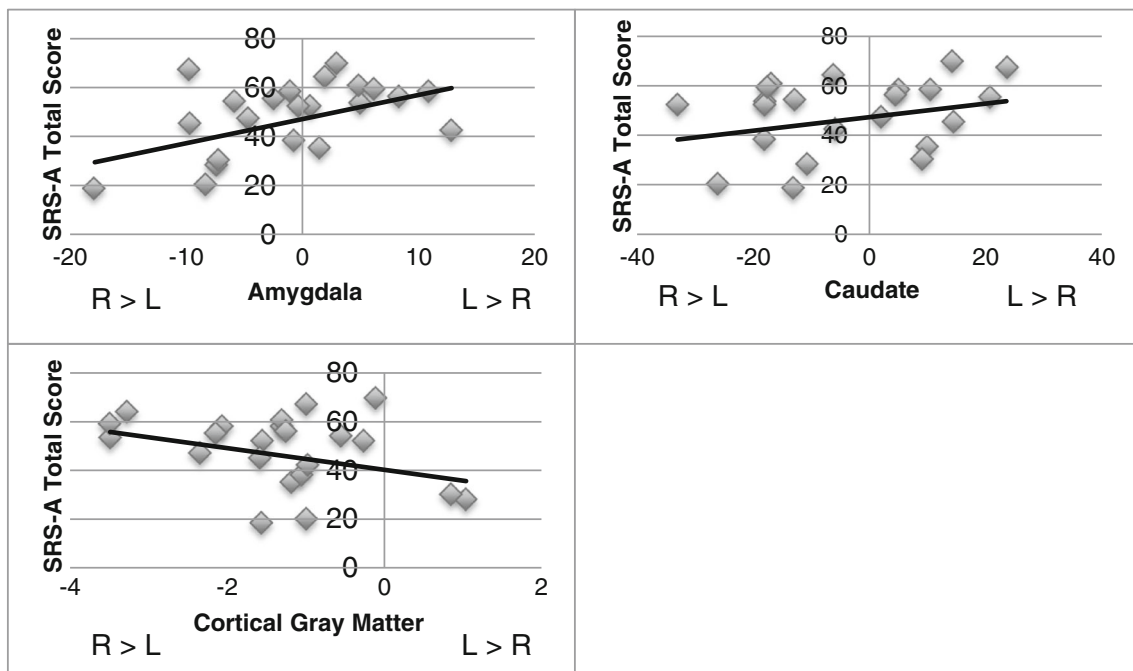


Fig. 1 SRS Scores are associated with leftward asymmetry of the amygdala and caudate, and rightward asymmetry of cortical gray matter

Recent confirmatory factor analytic work with the SRS indicates that the SRS comprises five factors (Frazier et al. 2014). We conducted model fitting for each of these factors to determine whether these factors differentially accounted for by brain volume and regional asymmetry. 55 percent of the variance in the Emotion Recognition subscale was explained by a model involving three regional asymmetries ($p < 0.001$). Increasing score in the Emotion Recognition domain was significantly related to rightward asymmetry of cortical gray matter ($\beta = -0.37, p < 0.05$), leftward asymmetry of the amygdalae ($\beta = 0.57, p < 0.01$), and leftward asymmetry of the caudate ($\beta = 0.16, p < 0.05$).

For Social Avoidance 31 % of the variance was explained by a model that included rightward asymmetry of cortical gray matter ($\beta = -0.44, p < 0.05$), leftward asymmetry of the caudate ($\beta = 0.56, p < 0.05$), and rightward asymmetry of the pallidum ($\beta = -0.61, p < 0.05$). The asymmetry models for Interpersonal Relationships, Insistence on Sameness and Repetitive Mannerisms approached ($p = 0.08$ and 0.06) but did not reach statistical significance. Similar model fitting analyses were conducted on the five subscales of the SRS using ICV-corrected regional volumes. Significant models were generated for both the Social Avoidance and Repetitive Mannerisms subscales. Increasing Social Avoidance scores were explained by decreasing proportion of cortical gray matter volume (Adjusted $R^2 = 0.18, \beta = -0.47, p < 0.05$). A significant model including decreasing hippocampal volume ($\beta = -0.56, p < 0.01$) predicted increasing scores on the Repetitive Mannerisms subscale (Adjusted $R^2 = 0.54, p < 0.001$).

The ICV-corrected regional volume models did not have a statistically significant effect on Interpersonal Relationships, Emotion Recognition, or Insistence on Sameness domains.

Discussion

Over the past several years, research has converged on a number of brain structures and functions that are implicated in the social and behavioral deficits and excesses observed in neurodevelopmental and neuropsychiatric disorders such as autism and schizophrenia. In this article we took a quantitative approach to these social and behavioral constructs in an effort to understand the brain-behavior links that underlie the normal range of social and behavioral traits that are associated with disorder. The findings suggest that many of the same brain regions that are implicated in ASD and other DBDs also account for normal variation of relevant behaviors. We believe that these findings support a broader, quantitative approach to understanding genes-brain-behavior links that are implicated in the context of normal and atypical behavior.

The Social Responsiveness Scale and the EQ/SQ scales are quantitative alternatives to traditional categorical diagnostic

measures that focus on specific behavioral traits associated with ASD. Such quantitative approaches enable us to study typical and atypical behavior as mutually informative. As Cicchetti (1984) noted: “We can learn more about the normal functioning of an organism by studying its pathology, and likewise more about its pathology by studying the normal condition” (p.1; Cicchetti 1984). This approach holds true not only for behavioral analysis, but also for brain-behavior links that underlie a variety of disorders.

Autism has been associated with several structural brain anomalies, including differential growth patterns and enlargement of the cerebellum, amygdala and hippocampus (Aylward et al. 2002; Carper and Courchesne 2005; Courchesne et al. 2001; Hashimoto et al. 1995; Hazlett et al. 2005; Herbert et al. 2004; Schumann et al. 2004; Sparks et al. 2002; see Dickstein et al. 2013 for a review). Increases in striatal volume (caudate and putamen) have also been reported in ASD, with a linear association observed between caudate and putamen volume and repetitive behavior (Hollander et al. 2005). Deviations from typical R>L asymmetry of these regions as well as disproportionate leftward asymmetry of cortical gray matter (Hazlett et al. 2005) are noted in ASD and other DBDs. These findings are not surprising given the role of these brain structures in learning, memory (hippocampus, caudate, cerebellum), emotion regulation and social functioning (hippocampus and amygdala), and motor control and repetitive behavior (cerebellum, caudate and pallidum). Whether these brain regions play a role in the normal distribution of ASD behavior in healthy subjects has not been fully explored.

In this study, we demonstrated that specific brain regions implicated in DBDs account for variance in several quantitative social, cognitive and behavioral traits in healthy subjects. Model-fitting indicated that a combination of limbic, striatal and cortical regions accounted for significant variance in social behavior and cognitive styles associated with disorders of DBD. As caudate and amygdala volumes deviate from the typical R>L asymmetry, and cortical gray matter becomes more R>L asymmetrical, overall SRS and Emotion Recognition scores increase. Social Avoidance was explained by a combination of cortical gray matter (rightward asymmetry), pallidum (rightward asymmetry) and caudate (deviation from rightward asymmetry). Increased D-scores on the EQ-SQ, indicating greater systemizing relative to empathizing cognitive style, was explained by deviation from the typical R>L asymmetry of the caudate. Absolute cortical gray matter volumes (corrected for intracranial volume) was a significant predictor of Social Avoidance, whereas hippocampal volume predicted higher scores on the Repetitive Mannerisms subscale of the SRS.

Taken together these findings indicate that even in healthy subjects, deviations from the typical patterns of cerebral asymmetry are associated with variability in social behavior and repetitive movements that characterize the autism spectrum.

The asymmetry findings were strikingly consistent with the literature noting deviations from normal asymmetry in clinically-significant conditions, such as ASD and schizophrenia. Therefore, we conclude that symmetry/asymmetry indices of neural structures may be a relevant marker for identifying more subtle, sub-clinical manifestations of DBD. This represents potentially important information for those interested in establishing and examining biomarkers for persons who may not reach the clinical threshold for diagnostic classification, but who may exhibit prodromal clinical behaviors, or who may be considered at risk for developing neurodevelopmental and neuropsychiatric conditions by virtue of being the first degree relative of a proband.

In a typical population, it remains unclear whether these brain-behavior associations indicate maladaptive patterns of behavior. For example, with behavioral scores in the normal range, it is difficult to determine whether these levels of behavior reflect maladaptive functioning or simply the nature of shared variance between behavior and neural traits. However, the findings indicate that even subtle variations within the normal range of behavior are associated with variations in neural structures. This attests to the strength of the quantitative approach to clinical syndromes, as well as to the utility of well-designed measures that capture the subtle variations in behavior.

The volumetric findings we report are in contrast with the majority of the literature reporting increasing size of relevant structures in ASD (Hollander et al. 2005; Juranek et al. 2006; Langen et al. 2007; Munson et al. 2006), though there are exceptions (Saitoh et al. 2001). In these healthy subjects, the volumetric findings were in the opposite direction, indicating that smaller hippocampal and cortical gray matter is associated with relatively more ASD social and repetitive behaviors. As such volumetric indices may be less consistent as an endophenotypic marker for DBD. It is noted, however, that direct comparison of the volumetric findings presented here to the ASD population may be problematic in that overall and regional brain volumes vary significantly over the lifespan, with marked overgrowth observed early in development in ASD (Courchesne et al. 2003). Therefore, our study is limited by the reduced age range in our sample, which precludes developmental analysis. Future work in this area should be extended to larger samples across a wider range of ages. We note too that there may be some limitations in our model-fitting approach. Specifically, this regression approach presents a risk of over-fitting, especially with small sample sizes and with multiple dependent measures (Babyak 2004). Replication or refinement of these models will be a necessary next step, particularly for the models with significance levels near $p < 0.05$.

We note additional limitations to this research that calls for further examination. Other factors – such as neuronal density – that are related to, but distinct from volumetrics may have

differential effects on behavior in typical and atypical populations. In addition, absolute volume alone may be deceiving as it does not indicate connectivity between and among neural structures, and future work would do well to link quantitative behavioral measures to specific pathways that integrate these neural systems governing learning, memory, cognitive style, social behavior and motor control. Also unknown is the directionality of the brain-behavior links. Information about directionality would benefit from longitudinal studies that carefully monitor cognitive and behavioral changes to determine whether such changes are antecedents or sequelae of changes in neural structure or function. Animal models of social and repetitive behavior may be particularly useful for establishing cause and effect of brain-behavior links, whether through lesion techniques or the use of knockout/knock-in models of known genetic causes of ASD. Several of the findings reported as non-significant after correction for multiple comparisons approached statistical significance and it remains unknown whether these may have emerged as statistically significant predictors of behavior given larger sample sizes and more statistical power. We note too, the importance of further examination of brain-behavior links in patient populations, using quantitative trait measures that are sensitive to more subtle variations in behavior. Such work will help to better understand the continuities and discontinuities in typical versus patient populations. Finally, future work should include more objective measures of social and repetitive behavior to complement and validate self-report measures. This will be particularly important for studies on younger populations or those with intellectual disability.

In conclusion, we emphasize the importance of continued efforts to understand the continuities between the typical range of cognitive and behavioral traits and those that reflect symptoms of clinical pathology. Such efforts require an increasing appreciation of the similarities between behaviors that are considered “normal” and those that are considered “abnormal”, as well as an appreciation of the considerable overlap between various clinical syndromes that have traditionally been viewed as distinct, orthogonal clinical entities.

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