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Morphological differences in the mirror neuron system in Williams Syndrome

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Abstract

Williams syndrome (WS) is a genetic condition characterized by an overly gregarious personality, including high empathetic concern for others. Although seemingly disparate from the profile of autism spectrum disorder (ASD), both are associated with deficits in social communication/cognition. Notably, the mirror neuron system (MNS) has been implicated in social dysfunction for ASD; yet, the integrity of this network and its association with social functioning in WS remains unknown. Magnetic resonance imaging methods were used to examine the structural integrity of the MNS of adults with WS versus typically developing (TD) individuals. The Social Responsiveness Scale (SRS), a tool typically used to screen for social features of ASD, was also employed to assess the relationships between social functioning with the MNS morphology in WS participants. WS individuals showed reduced cortical surface area of MNS substrates yet relatively preserved cortical thickness as compared to TD adults. Increased cortical thickness of the inferior parietal lobule was associated with increased deficits in social communication, social awareness, social cognition, and autistic mannerisms. However, social motivation was not related to anatomical features of the MNS. Our findings indicate that social deficits typical to both ASD and WS may be attributed to an aberrant MNS, whereas the unusual social drive marked in WS is subserved by substrates distinct from this network.

Keywords

William syndrome; social neuroscience; mirror neuron system; social cognition; social communication

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Introduction

Williams syndrome (WS) is a neurodevelopmental disorder characterized by a hemizygous genetic deletion on chromosome 7q11.23 (Ewart et al., 1994), and holds a prevalence rate of approximately 1 in 7,500 births (Stromme et al., 2002). The behavioral phenotype associated with WS includes an unusual hypersocial personality, manifested by an inclination to approach strangers, social disinhibition, hypervigilance to social stimuli (e.g., faces), and increased empathy towards others (Bellugi et al., 2000; Järvinen et al., 2013). Despite generally performing within the range of mild to moderate impairment in tests of intellectual functioning (Searcy et al., 2004), individuals with WS exhibit an increased use of language exclusively for social purposes as compared to typically developing (TD) individuals and those with other neurodevelopmental disorders (Järvinen-Pasley et al., 2008; Reilly et al., 2004). Individuals with WS are reportedly higher on the Social Closeness trait, a personality attribute pertaining to the desire to develop close relationships with others and to belong to a social group (Klein-Tasman & Mervis, 2003; Ng et al., in press). Together, the well-established genetic profile underpinning WS affords scientists to employ this syndrome as a model to determine the link among genes, neural systems and phenotypic behaviors that subserve human sociability and subsequently, disorders associated with social dysfunction.

Considered as a neurodevelopmental condition on the opposing social spectrum, ASD is associated with increased social withdrawal, restricted interests and repetitive behaviors, poor social reciprocity, and reduced use of empathetic gestures (APA, 2000; Baron-Cohen & Wheelwright, 2004; Charman et al., 1997; Lord et al., 2000). In contrast to WS, those with ASD are consistently documented to exhibit reduced social orientation coupled with heightened attention toward non-social stimuli when compared to TD individuals and other developmental disorders (i.e., individuals with Down syndrome or non-ASD developmental delays)(Dawson et al.; 1998; Klin et al., 2009; Swettenham et al., 1998). An eye-tracking study by Riby and Hancock (2009) examined face gaze patterns of individuals with ASD and WS in comparison to TD peers matched on nonverbal ability. These authors reported that individuals with ASD showed an overall reduced face gaze relative to their TD comparison participants and were slowed in detecting faces embedded in scenic stimuli. In contrast, those with WS showed an abnormally prolonged gaze towards a face and identified the hidden face with similar latency as TD counterparts. Consequently, on a superficial level, those with ASD and WS appear to deviate on the extreme ends of the spectrum of human sociability.

Although WS and ASD appear to be characterized by distinctive social phenotypes, both conditions share common social cognitive and communicative deficits that underlie their unusual social overtures. Children with WS and ASD are associated with significant deficits in social reciprocity and joint attention (Klein-Tasman et al., 2007; Klein-Tasman et al., 2009). Notably, individuals with ASD or WS similarly experience difficulties with the capacity to impute, recognize, and understand mental states of others, and the ability to apply this information in sequential social interactions (Tager-Flusberg & Sullivan, 2000). Klein-Tasman et al. (2010) administered the Social Responsiveness Scale (SRS; Constantino & Gruber, 2005), an inventory that evaluates social domains (e.g., social cognition, social communication, social motivation, social awareness, autistic mannerisms) that are

commonly deficient in children with ASD, to parents and teachers of children with WS. These researchers found that over half of their 49 children with WS scored in the clinically significant range on all sub-indices of the SRS with the exception of social motivation. Consequently, these social-cognitive and communicative perturbations may pose as common risk factors that contribute to their struggles in developing and sustaining peer relationships (Bauminger & Kasari, 2000; Gosch & Pankau, 1994).

The mirror neuron system (MNS), a neural substrate dedicated to the observation, imitation, decoding, and implementation of actions (Rizzolatti & Craighero, 2004) and inferring mental states (Iacoboni et al., 2005), has been extensively studied in ASD population and is implicated in their social deficits. It has recently been theorized that the aberrant social behaviors associated with WS may stem from dysfunction in circuits within this system (Järvinen et al., 2013). The MNS is a neural network that includes the interior frontal gyrus (IFG; i.e., pars opercularis), superior temporal sulcus (STS), and the inferior parietal lobule (IPL)(Van Overwalle & Baetens, 2009). Seminal investigations showed that the MNS activates in response to observation and imitation of biological motions (Gallese et al., 1996; Rizzolatti et al., 1996; Rizzolatti et al., 1999). Theories regarding the social functional correlates of MNS have been extended, linking imitation and mirror neurons with the ability to empathize rather than just the basic capacity to interpret motor actions (Gallese, 2001; Iacoboni, 2009).

Within ASD literature, abnormal structural integrity and anomalous connectivity of the MNS have been associated with increased severity of ASD symptomatology, particularly in terms of reduced social functioning. Hadjikhani and coauthors (2006) applying magnetic resonance imaging (MRI) methods observed cortical thinning of MNS structures in those with ASD, which was correlated with ASD symptom severity. In a similar vein, Wallace and colleagues (2012) also found associations between cortical thinning of STS and IPL and social dysfunction, as measured by total score on the SRS. Investigations of functional MRI with individuals with ASD have also revealed hypoactivity in the IFG (i.e., pars opercularis), when observing and imitating affective faces (Dapretto et al., 2005); however, during observations of hand movements, this same substrate was hyperactive in those with ASD relative to TD peers (Martineau et al., 2010). Enticott et al. (2010) employing transcranial magnetic stimulation technique further provided evidence of an association between hypoactivation of the MNS, in particular the IFG, with greater self-reported impairments in relating to others in social contexts. Moreover, a recent functional connectivity MRI investigation (Fishman et al., 2014) found that individuals with ASD showed atypical over-connectivity between the MNS and substrates involved in theory of mind (i.e., medial prefrontal cortex, temporal-parietal junction, posterior cingulate cortex), which was associated with their severity of social dysfunction as indexed by the social scores in the ADI-R. In aggregate, morphological and functional abnormalities of the MNS, and the communicative efficiency of this network with other social cognitive systems in the prefrontal region have been explicated as subserving the social dysfunction in ASD.

Recently, research has garnered more interest in the MNS as a possible driving factor of prosocial predisposition associated with WS (see Järvinen et al., 2013); however, to our knowledge, investigations directly examining the MNS structures and its association with

social function have not been conducted with individuals with WS. Behavioral experiments suggest that individuals with WS show greater empathetic concern towards strangers in distress when compared to cognitive-matched peers with Prader-Willi syndrome (c.f., Tager-Flusberg & Sullivan, 2000). Sparaci et al. (2012) found dissociations between the understanding of motor behaviors versus intent in those with WS. The participants with WS produced more inaccurate recognition of actions in images (e.g., What is she doing?) versus identification of the motor intention (e.g., Why is she doing it?); rather, their ability to infer the motive behind actions was mental-age appropriate. These findings were highlighted to contrast with those of Bora and colleagues (2009), which showed that individuals on the higher functioning end of ASD demonstrate intact motor understanding/recognition, but impaired ability to determine motor intent. Consequently, evidentiary support commonly point to the possibility of abnormalities with the anatomy or function in the MNS that are driving the social peculiarities associated with WS.

Considering that individuals with WS and ASD paradoxically manifest similar deficits in social functioning (e.g., theory of mind, communication) yet diverge in other aspects of social behavior (e.g., empathy), the present study aimed 1.) to investigate the anatomical integrity of the MNS in adults with WS relative to TD individuals by employing morphometric MRI methods and 2.) to evaluate the relationship between the MNS structures and areas of impaired social functioning on the SRS, an inventory typically used to assess social deficits common to ASD. Based on the exaggerated pro-social tendencies in WS and the extant literature linking social dysfunction with cortical thinning of the MNS in ASD, we hypothesized that this neural substrate would similarly differ in cortical thickness in individuals with WS relative to TD individuals. In a similar vein, we predicted that the structural integrity of this network to be associated with competency in social reciprocity.

Methods

Participants

A total of 36 adults participated in the present study: 20 individuals with WS and 16 TD comparison individuals (see Table 1 for participant characteristics). The groups did not significantly differ in chronological age (CA)(t(34)=1.98) and gender distribution (χ^2(1)=1.80, *ns*). Participants were recruited through the Laboratory for Cognitive Neuroscience at the Salk Institute for Biological Studies as part of a longstanding multisite program project. Participants with WS were administered the fluorescent in situ hybridization test to confirm for the deletion of the elastin gene, diagnostic of the condition (Korenberg et al., 2000). The TD comparison individuals were screened to ensure all were native English speakers. Participants were screened to ensure the absence of any history with neurological trauma, past or current psychiatric illness, and developmental or learning disabilities. The study protocols were approved by the Institutional Review Board at the Salk Institute and at the University of San Diego, California.

The participants were administered a test of intellectual functioning. Adults with WS were administered the WAIS-III (Wechsler, 1997), in continuation of the previous program project cycle. The TD comparisons were administered the WASI (Wechsler, 1999), as they were only participating in the current study and to maintain the brevity of our testing

session. Results were in agreement with previous reports (Searcy et al., 2004); those with WS scored lower on the VIQ, PIQ, and FIQ relative to their TD peers ($ps > .001$).

To examine areas of social functioning in individuals with WS that may be commonly compromised in ASD, the adult version of Social Responsiveness Scale (SRS; Constantino & Gruber, 2005) was administered to the caregivers of the participants with the syndrome. The SRS consists of 65 items rated on a 5-point Likert scale that marks the presence and severity of autistic symptoms in typical social exchanges. Possible ratings range from 1 (*not true*), 2 (*sometimes true*), 3 (*often true*), to 4 (*almost always true*). The five subscales that constitute the SRS Total index, a composite T-score, includes Social Awareness, Social Cognition, Social Communication, Social Motivation, and Autistic Mannerisms. The higher rating an individual receives across each scale, the more severe and greater symptom endorsement the child demonstrates. Social Awareness evaluates the extent a child demonstrates difficulties understanding others' mental states and perspective-taking. Social Cognition generally assesses deficiencies in social information processing; whereas, Social Communication measures the extent the participant shows impairment in expressing and understanding others' speech. Social Motivation indexes broad deficits in the individuals' initiation of social exchanges and drive to engage others socially. Autistic Mannerisms examines the extent the individual exhibits repetitive behaviors, obsession with unusual interests, and heightened sensory experiences. Individual subdomains of the SRS yield raw scores that are then transformed to T-scores differentially by gender, in accordance to the SRS score conversion protocol. All participants received the adult versions (ages 19 years and older) with the exception two TD participants who were offered the child/adolescent version (age normed from 4 to 18 years). Of importance, the validity of the SRS has been established against the widely applied Autism Diagnostic Interview-Revised (ADI-R) (Constantino et al., 2003).

MRI Data Acquisition

A 1.5 Tesla GE Signa HDx 0M5 TwinSpeed scanner (GE Healthcare, Wukesha, WI) was employed to acquire the high resolution T1-weighted MRI scans (echo time = 3.0 msec, repetition time = 8.7 msec, inversion time = 270 msec, flip angle = 8°, delay time = 750 msec, bandwidth = ± 15.63 kHz, field of view = 24 cm, matrix = 192 × 192, voxel size = 1.25 × 1.25 × 1.2 mm). Given individuals with WS endorse significant fears and anxieties (Dykens, 2003), additional measures were applied to ensure the utility and reliability of the images obtained. Real-time, prospective motion tracking and correction (PROMO) was applied with spiral navigator pulse sequences and an extended Kalman filter algorithm (Roddey et al., 2003; Shankaranarayanan et al., 2007; White et al., 2010), as an effort to correct artifacts produced by head motion, and improve reliability of morphological indices (Brown et al., 2010; Kuperman et al., 2011). Application of PROMO improves the diagnostic utility of the MRI data obtained particularly in clinical populations and younger age groups that struggle with the situational contexts and demands of scanning procedures (Brown et al., 2010; Kuperman et al., 2011).

MRI Data Preprocessing

The methods implemented to process the data are in congruence to that reported in Brown et al. (2012). Briefly, correction for heterogeneity of the imaging was conducted with the FreeSurfer software suite (version 3.0.5; http://surfer.nmr.mgh.harvard.edu). Three-dimensional reconstruction of cortical surfaces was completed by using the MRI data with well-documented algorithms applied in prior research (Dale et al., 1999a; 1999b; Fischl et al., 2002). Finally, the boundary between gray and white matter was approximated and narrowed using the reconstructed model, and the surface of the model was then warped towards the pial surface. Finally, the index of cortical thickness was obtained by measuring the shortest distance between the white matter surface to the pial surface across all cortical points.

Regions of Interest (ROIs)

The IFG (i.e., pars opercularis), STS, and IPL constituted the MNS region of interest. Particularly, the parcellations were selected based on extensive research consistently reporting the activation of these regions in response to mirror neuron tasks across TD population and those with ASD (e.g., observation of biological movements, decoding of actions, inferring intentions of motoric movements)(see Oberman & Ramachandra, 2007 for a review).

Statistical Analysis

Analysis of covariance (ANCOVAs) were employed with group (WS/TD) as the fixed factor and total cortical surface area or thickness as covariates. Descriptive analyses were completed by examining the proportion of the participants with WS that met clinical threshold per SRS index based on the SRS scoring manual. Notably, higher SRS T-scores reflect greater deficits within the respective domain. Spearman's rank-order coefficient correlations were conducted to examine the associations between ROIs and SRS subdomains (Social Awareness, Social Communication, Social Cognition, Social Motivation, Autistic Mannerisms). Bonferonni correction threshold of .017 was applied to account for the number of ROIs examined.

Results

MRI Analyses

The inclusion of age as a covariate did not significantly change results, thus it was excluded from the following analyses. ANCOVAs revealed that cortical thickness in the left STS, $F(1,33) = 6.37$, $p = 0.017$, and right pars opercularis, $F(1,33) = 6.48$, $p = 0.016$, are reduced in participants with WS relative to TD individuals. Cortical thickness of the right IPL was greater in TD than in the WS group, $F(1,33) = 5.40$, $p = 0.026$; however; the effect was not significant when applying the multiple comparison correction. In contrast, multiple regions were observed to differ across groups in cortical surface area (see Table 2). Cortical surface areas of bilateral pars opercularis and IPL were reduced in those with WS over that of TD comparison individuals, $Fs > 6.46$, $ps < 0.016$. The TD comparisons also yielded more pronounced left cortical surface area of STS than those with WS, $F(1,33) = 7.19$, $p = 0.011$.

Altogether, the morphological structures of the MNS are profoundly impoverished in those with WS.

SRS Measure and WS

According to the SRS scoring procedures, a T-score of 59 or below is non-diagnostic and considered typical, 60 to 75 is mild to moderate symptomatology often common to high functioning autism, and 76 and above is severe clinical status of ASD. Figure 1 illustrates the percent of the WS participant group scoring clinically significant within each domain of the SRS. Approximately half or more of our participants with WS endorsed mild to severe symptoms in Social Awareness, Social Cognition, Social Communication and Autistic Mannerisms; however, majority of these individuals were asymptomatic within the measure, Social Motivation. Similarly, the average SRS T-scores obtained by these participants also reflected a mild to severe symptomatology endorsement of all putative sub-measures with the exception of Social Motivation (see Table 1). Taken together, individuals with WS share significant social disturbances commonly observed in those with ASD.

Associations between Anatomical Structure of MNS and Social Functioning in WS

Associations between general intellectual functioning with both anatomical measures of MNS substrates did not reach significance when the criterion was applied. No significant correlations between cortical surface area and SRS indices were found, with an exception of a negative association between right STS and Autistic Mannerisms, $r_S(18)=-0.53$, $p =0.024$, which did not meet our correction criterion. In contrast, cortical thickness, specifically of left IPL, and social communication and cognition emerged, $rs > 0.68$, $ps < 0.005$ (see Table 3). Significant correlations were observed between thickness of IPL and Social Awareness and Autistic Mannerisms, $rs > 0.47$, $ps < .05$; however, they did not meet our criterion when we applied a conservative approach. Thus, a general pattern of increased cortical thickness in the IPL was related to reduced social dysfunction pertaining to awareness, cognition, communication, repetitive behaviors and limited interests; however, the social drive to engage with others remains distinct from anatomical integrity of the MNS substrates.

Discussion

The present study showed that, similar to findings in ASD (Hadjikhani et al., 2006), the cortical surface area of the MNS network is reduced in individuals with WS relative to TD participants. However, in sharp contrast to those with ASD (Hadjikhani et al., 2006), greater cortical thickness of the IPL was robustly related to severity of social deficits in adults with WS. However, Social Motivation was found to be independent of the anatomical integrity of MNS substrates. Taken together, our results imply that the integrity of the MNS substrates is impoverished in those with WS, and that the development of this network likely contributes to the social dysfunction that such individuals have in common with those diagnosed with ASD. At the same time, it appears that the social drive for WS may be distinct from this system.

The reduced cortical surface area of STS, IFG and IPL in individuals with WS is consistent with the extant literature documenting aberrant processing of and responsivity to social

information (i.e., increased attention towards social stimuli; Riby & Hancock, 2008, 2009). Haxby et al. (2000) proposed that the STS is part of a distributed neural network, dedicated to face perception, with an intimate involvement in the perception of face movement/ orientation and localized facial attributes (e.g., eyes, mouth). Additionally, STS has reciprocal connections with the amygdala, permitting hypervigilance of both regions in response to social stimuli (see Allison, Puce, & McCarthy, 2000 for review). Taken together, the STS assumes a prominent role in the initial social perceptual processes. Considering that individuals with WS show a bias toward faces (Riby & Hancock, 2008, 2009), combined with relatively preserved functionality of face-processing neural regions including STS (Mobbs et al., 2004), it is possible that the connectivity of the STS with emotion-processing substrates drives the selective attention towards social stimuli. Consistent with this postulation, our results indicate that despite observations of morphological differences in the STS between individuals with WS and TD, associations between the structure characteristics and social deficits did not emerge within those with WS, suggesting that the dysfunction does not stem from those substrates alone.

In a similar vein, our results showed that relative to TD counterparts, those with WS have less cortical surface area and thickness of the IFG, a substrate linked to emotional empathy (Kaplan & Iacoboni, 2009; Shamay-Tsoory et al., 2009). Shamay-Tsoory and authors (2009) contended that empathy comprised of emotional empathy, supported by IFG, and cognitive empathy, largely attributed to ventromedial prefrontal cortex. They distinguished emotional empathy as the ability to empathize affectively (e.g., feel how others feel), and cognitive empathy as the ability to understand the conspecifics' state (i.e., mentalization, perspective-taking). Brain imaging investigations have shown that the IFG of TD adults activates when these individuals imagine others' pain (Lamm, Decety, & Singer, 2011), and complete empathic evaluations in social reasoning tasks (Farrow et al., 2001). Although the IFG has not been explored in neuroscientific studies in individuals with WS, particularly with interpersonal measures, numerous studies have shown that individuals with WS manifest exaggerated empathetic gestures (Tager-Flusberg & Sullivan, 2000), empathic personality traits (Klein-Tasman & Mervis, 2003), and elevated social-emotionality, including frequent displays of empathetic verbal expressions (Doyle et al., 2004). Currently it is unclear whether the empathy experiences by those with WS may be qualitatively different than that under normative development, e.g., these individuals feel others' emotions intensely versus react/respond to others emotions strongly. Nonetheless, our results contribute to the growing literature by implicating the MNS in the prosocial behaviors in individuals with WS.

It should be noted that the lack of associations between the anomalous STS and IFG morphology with social measures might reflect perturbations in the communication across social networks, rather than abnormal functioning of these individual regions alone. For example, a recent investigation of individuals with ASD documented the association between the overabundant connectivity between their MNS and their social cognitive neural network with their symptom severity (Fishman et al., 2013). It is plausible that in WS the neural organization of the MNS with other social cognitive networks is fundamentally different. Given that both results of the current study and those of past studies consistently show that WS individuals endorse overlapping symptoms with ASD peers (Klein-Tasman et al., 2007, 2009) yet diverge in prosocial attributes and social appetitive drive, investigative

efforts towards the organization of the neural networks related to social perception may better explicate their gregarious profile.

Our main finding showed that the IPL of individuals with WS differs anatomically from that seen in TD individuals. The IPL is a nexus with connections to somatosensory, visuospatial and visuomotor processing regions in the brain, and differentially receives input from superior colliculus, cerebellum and hippocampus (see Clower et al., 2001 for a review). As such, functions regarding to IPL vary depending on the subregion of interest as well as its circuitry with neighboring cortical and subcortical areas. However, numerous investigations of the IPL have focused on its role in action awareness, planning and intentionality (Fogassi et al., 2005; Desmurget & Sirigu, 2012). In a recent review, Desmurget and Sirigu (2012) posited that the IPL operates uniquely during the subjective desire to move and is antecedent to the planning of motor actions. In brief, the IPL may be more involved with the drive underlying actions, rather than strategy formulation. Based on the recent postulations of the IPL's early role in the initial sequence of action desire to action implementation, anomalies in the IPL within WS may have a role in their unconventional interpersonal behaviors (e.g., unexpected affectionate gestures; Davies et al., 1998) and increased social engagement with strangers (Doyle et al., 2000, Frigerio et al., 2006; Jones et al., 2000). Specifically, the impetus to act in social situations in individuals with WS combined with their weak inhibitory control and executive skills (e.g., planning; Menghini et al., 2010) may then result in abnormal social overtures.

Importantly, our results showed that increased cortical thickness in individuals with WS is most strongly associated with deficits in Social Cognition and Social Communication. Limited studies show that the IPL activates specifically when simulating movements from others' perspectives rather than in response to self-produced actions (see Blakemore & Frith, 2003 for a review). This notion was recently supported by results of a transcranial magnetic stimulation study in which simulated lesions on the right IPL led to substantial disturbances in discrimination of self- versus others-faces (Uddin et al., 2006) and an imaging study where self-recognition activated both IPL and IFG (Uddin et al., 2005). Together, the IPL is involved in the self-other differentiation process. As such, in WS individuals, abnormal cortical surface area of their IPL may disrupt this discrimination process, which could explain their poor ability to mentalize (Porter et al., 2008; Sullivan & Tager-Flusberg, 1999; Tager-Flusberg & Sullivan, 2000), to use pragmatic speech (Laws & Bishop, 2004), and to engage in joint attention (Laing et al., 2002).

Additionally, our observed associations between increased cortical thickness of the IPL and social deficiencies in adults with WS warrant further longitudinal investigation. Under typical development, cortical thickness increases profoundly in the first two years of life (Lyall et al., 2014). Subsequently, distinct brain regions undergo cortical thickening, albeit at decreased rate, and cortical thinning to shape the brain based on ones' experiences. In contrast, surface area continues to expand significantly up to puberty (Lyall et al., 2014). As such, examining the neurodevelopmental mechanisms involved in the "social brain" of WS individuals may offer critical information as to how lower-level neural dysfunction cascades into increasingly deviating interpersonal behaviors over time. Particularly, those with WS demonstrate a hyper-social drive as early as infancy (Frigerio et al., 2006; Jones et al.,

2000); and, as these individuals mature, their neural systems are likely to gradually modify in structure, function and organization through experience-dependent processes (Greenough et al., 1987). Therefore, it may be possible that the observed associations differ when examined during the first few years of life, relative to adulthood. However, these possibilities are conjectures and have yet to be explored.

It is important to further emphasize that while our findings implicate the role of MNS system in social reciprocity, other neural regions likely contribute to the atypical social profile of WS. Of note, social motivation, the domain found most "typical" in those with WS on the SRS (Klein-Tasman et al., 2010), was not related to MNS morphology in the current study, raising caution about attributing social dysfunction solely to this network (Fan et al., 2010; Southgate & Hamilton, 2008). It has been proposed that mirror neurons of varied MNS neural substrates contribute to social functions differentially, complicating the links between this network and interpersonal behaviors (Williams, 2008). New research has suggested that MNS in ASD is not globally defective, as these individuals produce similar levels of MNS activity relative to TD peers during observations of interactive or individual hand actions (Enticott et al., 2013). Therefore, more research will be needed to understand the extent to which the MNS specifically contributes to social functioning (e.g., prosociality, social attunement, imitation, etc.) in WS.

Despite our novel findings, several limitations will need to be addressed in subsequent research. The present study examined morphological differences in MNS substrates solely between individuals with WS and TD. However, the inclusion of a second cognitive-matched comparison would be useful in determining whether such perturbations are common to general populations with developmental disabilities, or exclusive to WS. Additionally, our study employed the SRS, which assesses broad interpersonal skills, as a measure of social functioning. However, the use of such inventories with general indices can constrain the interpretation of results. Although WS and ASD share deficits within social domains (e.g., social communication), these may stem from diverging behaviors (e.g., reduced verbal expression but goal-directed versus high expressivity that is devoid of pragmatic meaning/understanding). Thus, applying social measures that represent real-life behavior reliably would serve as a stronger index of interpersonal functioning. In effect, while the social behavioral traits of WS are relatively well-documented, more detailed and multi-level approaches will be necessary to better understand 'the social brain' of WS (cf. Haas & Reiss, 2012; Järvinen et al., 2013).

The central goal of the present study was to examine the morphological integrity of the MNS in WS and its association with social deficits that are common to both WS and ASD. Our findings showed that the cortical surface area of the MNS in individuals with WS is reduced relative to TD individuals, consistent with previous research with adults with ASD (Hadjikhani et al., 2006). However, while cortical thinning of the MNS was linked to social dysfunction in ASD (Hadjikhani et al., 2006), greater cortical thickness of the IPL was uniquely associated with the similar impairments in WS with the exception of social motivation. Our results suggest that the MNS in its entirety may not be accountable for the social deficits in those with WS. Rather, functional connectivity among social networks may subserve the dysfunction. Finally, the lack of association between the MNS structures and

the propensity to interact with others in WS indicates that the appetitive drive may result from a more complex, distributed network within the brain rather than focal systems. In effect, the shared social dysfunction in WS and ASD may be subserved by differential neuropathological correlates.

Acknowledgements

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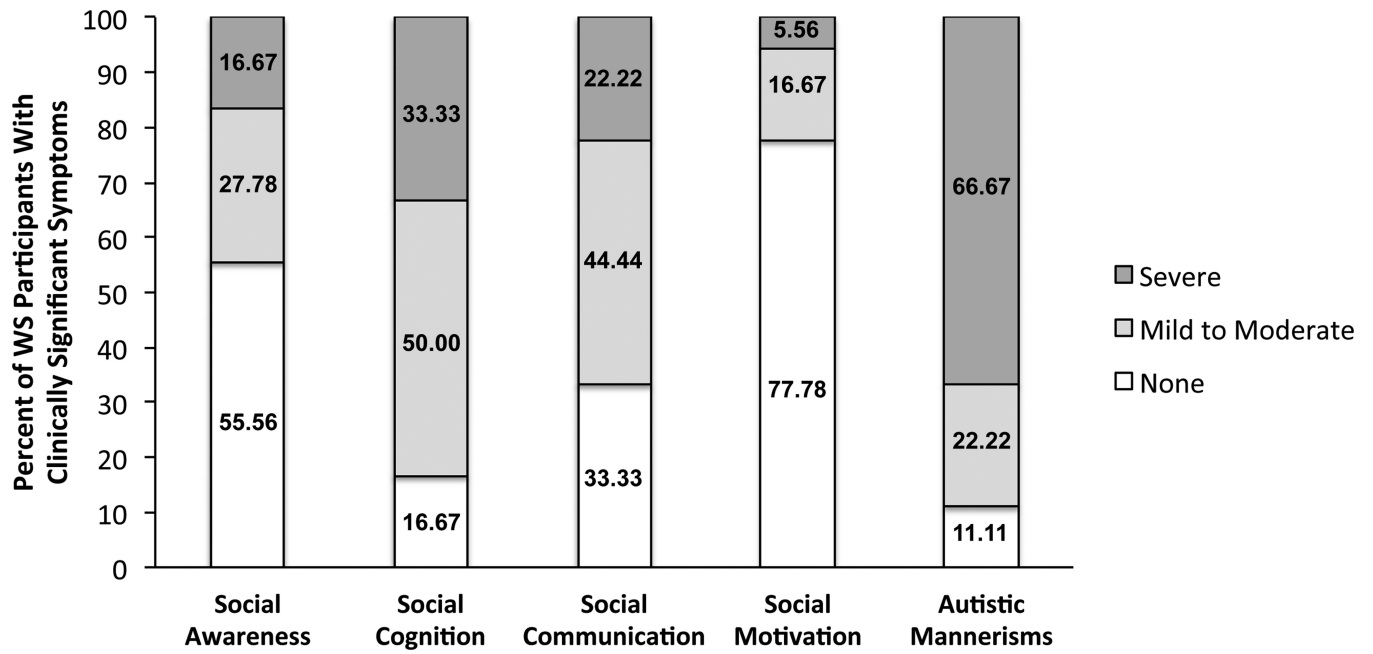
Figure 1.
Percentage of participants with WS (N = 18) meeting clinical threshold across the SRS.

	Mean (SD)[Range]	
	Williams Syndrome (N=20)	Typical Development (N=16)
Age (years)	32.2(11.2) [19.0-56.9]	25.9(6.8) [19.0-43.1]
Sex	8F	10F
Caucasian (%)	85.0%	62.5%
Handedness	16R, 4L	13R, 3L
VIQ	71.5(5.7)	96.8(15.7)
PIQ	65.5(5.2)	96.8(15.0)
FIQ	66.2(6.3)	96.7(14.6)
SRS Total (T-scores)	67.1(11.3)	---
Social Awareness	59.3(12.0)	---
Social Cognition	69.9(14.4)	---
Social Communication	63.6(11.6)	---
Social Motivation	54.0(10.6)	---
Autistic Mannerisms	79.4(14.5)	---

Note. The Social Responsiveness Scale (SRS) was administered only to caregivers of WS participants. Two of the twenty caregivers did not complete the inventory.

	Williams Syndrome (N=20)	Typical Development (N=16)	p-values
Cortical Thickness (mm)			
Pars opercularis (r/l)	2.68 / 2.69	2.77 / 2.73	0.016 [*] / 0.205
Inferior parietal lobule (r/l)	2.60 / 2.60	2.66 / 2.62	0.026 [*] / 0.548
Superior temporal sulcus (r/l)	2.96 / 2.97	2.93 / 2.89	0.347/ 0.017 [*]
Cortical Surface Area (mm²)			
Pars opercularis (r/l)	1075.75 / 1219.40	1477.50 / 1649.50	0.016 [*] / 0.003 [**]
Inferior parietal lobule (r/l)	4336.95 / 3763.55	5615.25 / 4679.31	0.003 [*] / 0.014 [**]
Superior temporal sulcus (r/l)	3059.15 / 3257.75	3508.88 / 3617.00	0.577 / 0.011 [*]

[***] $p < .001$

[*] $p < .05$

[**] $p < .01$

Cortical Thickness (mm)	Social Awareness	Social Cognition	Social Communication	Social Motivation	Autistic Mannerisms
Right					
Pars opercularis	0.29	0.30	0.09	−0.38	0.01
Inferior parietal lobule	0.47*	0.45	0.54*	−0.13	0.27
Superior temporal sulcus	0.36	0.16	0.32	−0.14	0.18
Left					
Pars opercularis	0.17	−0.17	0.22	0.13	0.09
Inferior parietal lobule	0.53*	0.68**	0.68**	0.14	0.53*
Superior temporal sulcus	0.38	0.21	0.44	0.09	0.23

***$p < .001$

Note. Higher T-scores on SRS reflect greater impairment within the domain.

*
$p < .05$

**
$p < .01$