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Cerebellar gray matter and lobular volumes correlate with core autism symptoms

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ABSTRACT

Neuroanatomical differences in the cerebellum are among the most consistent findings in autism spectrum disorder (ASD), but little is known about the relationship between cerebellar dysfunction and core ASD symptoms. The newly-emerging existence of cerebellar sensorimotor and cognitive subregions provides a new framework for interpreting the functional significance of cerebellar findings in ASD. Here we use two complementary analyses — whole-brain voxel-based morphometry (VBM) and the SUIT cerebellar atlas — to investigate cerebellar regional gray matter (GM) and volumetric lobular measurements in 35 children with ASD and 35 typically-developing (TD) children (mean age 10.4 ± 1.6 years; range 8–13 years). To examine the relationships between cerebellar structure and core ASD symptoms, correlations were calculated between scores on the Autism Diagnostic Observation Schedule (ADOS) and Autism Diagnostic Interview (ADI) and the VBM and volumetric data. Both VBM and the SUIT analyses revealed reduced GM in ASD children in cerebellar lobule VII (Crus I/II). The degree of regional and lobular gray matter reductions in different cerebellar subregions correlated with the severity of symptoms in social interaction, communication, and repetitive behaviors. Structural differences and behavioral correlations converged on right cerebellar Crus I/II, a region which shows structural and functional connectivity with fronto-parietal and default mode networks. These results emphasize the importance of the location *within* the cerebellum to the potential functional impact of structural differences in ASD, and suggest that GM differences in cerebellar right Crus I/II are associated with the core ASD profile.

1. Introduction

Autism spectrum disorders (ASDs) are characterized by impairments in social interaction, communication, and restricted or repetitive behaviors and interests (DSM-IV: American Psychiatric Association, 1994). Neuroimaging research has revealed a broad network of regional brain abnormalities in ASD, including frontal, parietal, and limbic regions, the basal ganglia, and the cerebellum (Amaral et al., 2008). Cerebellar structural and functional differences are consistently reported in ASD, suggesting that cerebellar dysfunction may be important in the etiology of the disorder (Allen et al., 2004; Courchesne, 1997; Fatemi et al., 2012). Supporting this, almost all post-mortem analyses of ASD individuals have reported reduced Purkinje cell size and number regardless of age, sex, or cognitive ability (Bailey et al., 1998; Bauman and Kemper, 2005; Fatemi et al., 2002; Whitney et al., 2009). Although neuroimaging meta-analyses suggest that several different regions of the cerebellum are affected in ASD (Duerden et al., 2012; Stoodley, 2014; Yu et al., 2011), no study has used both voxel-based and lobular region of interest analyses to examine structural differences within the cerebella of autistic individuals, while also assessing the relationship between these cerebellar subregions and core ASD symptoms.

Anatomically, the cerebellum is divided into ten lobules (lobules I–X) and three lobes: the anterior lobe (lobules I–V), the posterior lobe (lobules VI–IX), and the flocculonodular lobe (lobule X; Fig. 1). Anatomical, clinical, and neuroimaging studies support the idea that regions within the cerebellum have functionally distinct roles in movement, cognition and affective processing (Stoodley and Schmahmann, 2010). Somatomotor representations of the body are found in the anterior lobe and lobule VIII, which interconnect with sensorimotor areas of the cerebral cortex and are engaged during sensorimotor tasks (Stoodley and Schmahmann, 2010). The large posterior lobe, including lobules VI and VII (which is subdivided into Crus I, Crus II and VIIB), receives input from prefrontal and parietal association areas and is engaged during cognitive tasks (Strick et al., 2009). Recent functional connectivity data show that the majority of the cerebellum is

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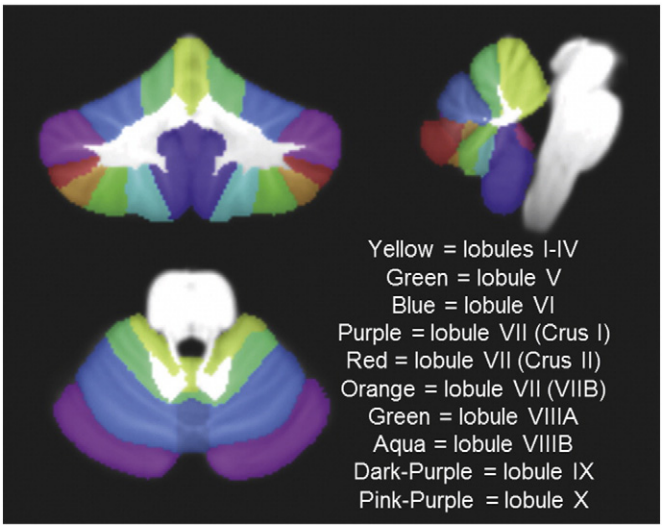

Fig. 1. The human cerebellum with lobules I–X color-coded. From the spatially unbiased infratentorial template [SUIT] of the cerebellum and brainstem (Diedrichsen et al., 2009; Diedrichsen, 2006).

functionally connected to association networks involved in cognitive and affective processes, rather than somatomotor networks (Buckner et al., 2011). Clinical outcomes also reflect the topography seen in healthy controls, as lesions involving posterior regions of cerebellum can lead to difficulties in executive functioning, language, memory and affect, while damage to the anterior cerebellum can result in motor impairments with minimal cognitive effects (Schmahmann and Sherman, 1998). Based on these data, the putative role of the human cerebellum has been expanded to include higher order cognitive and affective processes (Ito, 2008; Stoodley and Schmahmann, 2009; Strick et al., 2009). The unique patterns of connectivity of different cerebellar subregions result in a functional topography, whereby different regions process different types of information (Stoodley, 2012; Strick et al., 2009). This topography is of importance when considering the localization of cerebellar structural and functional differences in ASD, and may be beneficial in the interpretation of cerebellar findings in ASD.

Neuroimaging studies comparing ASD with typically developing (TD) individuals reveal differences in several regions of the cerebellum. Structural MRI studies have described hypoplasia of the posterior vermis in ASD (Carper and Courchesne, 2000; Courchesne et al., 1988, 1994, 2011; Murakami et al., 1989), and meta-analyses of voxel-based morphometry (VBM) studies have reported consistent gray matter (GM) decreases in right Crus I, lobule VIII, and lobule IX (Duerden et al., 2012; Stoodley, 2014; Yu et al., 2011). Decreased GM is less commonly reported in regions such as left Crus I, and sometimes overall increased cerebellar GM is noted (Duerden et al., 2012; Yu et al., 2011). Functional MRI studies have revealed reduced activation in the cerebellum in ASD during social, language, and motor tasks. Individuals with ASD underactivate Crus I while processing facial and vocal stimuli (Wang et al., 2007) and during executive functioning paradigms (Solomon et al., 2009). Language tasks elicit abnormal activation in lobule VII in autistic individuals during core aspects of communication such as semantic processing (Harris et al., 2006). Lastly, children with ASD fail to engage the anterior cerebellum (lobule IV/V) during motor tasks when compared to their TD peers (Mostofsky et al., 2009). While convergence across studies exists, there remains significant variation among cerebellar neuroimaging findings in ASD.

Clinical studies also report ASD-like symptomology in patients with cerebellar abnormalities. Malformations of the cerebellar vermis are associated with social and affective disorders, while cerebellar hemisphere malformations are linked to expressive language, gross motor, and executive functioning deficits, symptoms relevant to ASD (Bolduc et al., 2012; Tavano et al., 2007). Premature infants sustaining cerebellar damage have a 40-fold increase in positive ASD screens relative to controls (Limperopoulos et al., 2007). Further, individuals with Tuberous Sclerosis (TSC) have high rates of ASD symptoms (Gillberg et al., 1994; Hunt and Shepherd, 1993; Smalley et al., 1992; Wing and Gould, 1979) which have been specifically related to tubers located within the cerebellum (Weber et al., 2000).

The links between cerebellar dysfunction and ASD symptomology have led some to posit that autism might be a "disease of the cerebellum" (Rogers et al., 2013). However, few studies have examined the role of specific cerebellar subregions in autism, and even fewer have investigated correlations between regional GM and behavioral measures in ASD (Kosaka et al., 2010; Riva et al., 2013; Rojas et al., 2006). Thus far, most studies have examined differences at the hemispheric level, and studies investigating regional differences often have not localized findings to particular cerebellar lobules. Given the emerging functional topography of the cerebellum and the various cerebellar regions implicated in autism pathophysiology, it is important to investigate more discrete subdivisions within the cerebellum and to consider their functional relevance. The present study investigates cerebellar structure in ASD and links the structural findings to the core symptoms of the disorder.

To our knowledge, this is the first study to examine the cerebellum in autism at both a voxel-based and lobular level by using two complementary approaches — voxel-based morphometry (VBM) (Ashburner and Friston, 2000; Good et al., 2001) and the Spatially Unbiased Infratentorial Template (SUIT) (Diedrichsen et al., 2009; Diedrichsen, 2006) for lobular region of interest (ROI) volumetric analysis. Moreover, this is the first study to correlate cerebellar lobular volumes with behavioral measures. Unlike ROI approaches, VBM allows for a precise, voxel-level examination of the cerebellum in the context of the whole brain in an unbiased, operator-independent manner. Complementing this approach, the SUIT template and atlas allow for a ROI-based examination of cerebellar substructure by providing a high-resolution atlas and template of the human cerebellum and brainstem. The more commonly-used MNI template provides little contrast for the cerebellum and cerebellar structures, while the SUIT template preserves the anatomical detail of the cerebellum and allows for better localization of cerebellar findings. As lobules are anatomically (rather than functionally) defined, VBM can elucidate with millimeter resolution how structure is related to ASD symptomology without the confines of lobular boundaries, and might reveal GM differences that span or cross lobules. On the other hand, the SUIT ROI method provides an excellent template for measuring specific cerebellar lobules and may be more statistically powerful than the VBM approach; however, the more gross lobular measures might hide subtle GM differences between groups. Because there can be differences in results when voxel-based vs. ROI approaches are employed, using both of these techniques in the same dataset helps to establish structural differences that converge across analysis methods. Therefore, combining VBM and SUIT methods in the same dataset allows for an examination of the cerebellum at the voxel-level and lobular-level, capitalizing on the strengths of each approach. For both approaches, we examined the relationship between ASD symptoms and cerebellar structure.

2. Materials and methods

2.1. Participants

Seventy children aged 8–13 years participated in this study: 35 children with ASD (30 males; mean age = 10.4 ± 1.6 years; 32 right-handed, 3 left-handed) and 35 TD children (21 males; mean age = 10.4 ± 1.5 years; 32 right-handed, 2 left-handed, 1 mixed dominance). TD participants were age-matched to ASD subjects by closest age. When there were multiple exact or closest-aged TD participants,