Developmental Cognitive Neuroscience 24 (2017) 1–11

Contents lists available at ScienceDirect

Developmental Cognitive Neuroscience

journal homepage: http://www.elsevier.com/locate/dcn

The developmental relationship between specific cognitive domains and grey matter in the cerebellum

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ARTICLE INFO

Article history:
Received 16 July 2016
Received in revised form 17 October 2016
Accepted 9 December 2016
Available online 21 December 2016

Keywords:
Cerebellum
Developmental imaging
Cognition
Voxel based morphometry
PING
NIH toolbox

ABSTRACT

There is growing evidence that the cerebellum is involved in cognition and cognitive development, yet little is known about the developmental relationship between cerebellar structure and cognitive subdomains in children. We used voxel-based morphometry to assess the relationship between cerebellar grey matter (GM) and language, reading, working memory, executive function, and processing speed in 110 individuals aged 8–17 years from the Pediatric Imaging, Neurocognition, and Genetics (PING) Study. Further, we examined the effect of age on the relationships between cerebellar GM and cognition. Higher scores on vocabulary, reading, working memory, and set-shifting were associated with increased GM in the posterior cerebellum (lobules VI–IX), in regions which are typically engaged during cognitive tasks in healthy adults. For reading, working memory, and processing speed, the relationship between cerebellar GM and cognitive performance changed with age in specific cerebellar subregions. As in adults, posterior lobe cerebellar GM was associated with cognitive performance in a pediatric population, and this relationship mirrored the known developmental trajectory of posterior cerebellar GM. These findings provide further evidence that specific regions of the cerebellum support cognition and cognitive development, and suggest that the strength of this relationship depends on developmental stage.

1. Introduction

Neuroanatomical, clinical, and neuroimaging studies support the proposal that the cerebellum is involved in cognitive task performance. Much of the evidence linking cerebellar structure and function with cognitive performance is based on neuroimaging studies in adults (e.g., Hogan et al., 2011; Keren-Happuch et al., 2014; Stoodley and Schmahmann, 2009; Stoodley and Stein, 2012), yet the developmental unfolding of these relationships is not well understood. This is a timely issue, given the increasing appreciation of the role of cerebellar function during development (e.g., D'Mello and Stoodley, 2015; Stoodley, 2016; Wang et al., 2014) and mounting evidence for cerebellar structural and functional differences in several neurodevelopmental disorders (see Stoodley, 2014, 2016).

What might the cerebellum contribute to development? From a mechanistic perspective, the cerebellum is involved in various types of implicit/procedural learning (Ito, 2005, 2006; Timmann et al., 2010). Procedural learning may support new stages of representation throughout cognitive development (Karmiloff-Smith, 1995), and it has been proposed that procedural learning is impaired in several neurodevelopmental disorders, including autism and developmental dyslexia (see Ullman and Pullman, 2015). Indeed, differences in distinct cerebellar regions have been identified in autism, dyslexia, and ADHD (Stoodley, 2014). From a neural perspective, it has been proposed that the cerebellum may be crucial to the optimization of both structure and function in the developing brain (see Wang et al., 2014; D'Mello and Stoodley, 2015; Stoodley, 2016). Wang et al. (2014) suggested that the cerebellum is involved in setting up the specialization of cortical regions involved in cognitive processes, and hence could have a crucial organizing effect during development. Unlike the cerebral cortex, in which earlier damage allows for compensatory plasticity (Kolb and Gibb, 2007), cerebellar damage earlier in life can result in worse cognitive outcomes (Davis et al., 2010), leading to long-term deficits

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http://dx.doi.org/10.1016/j.dcn.2016.12.001
1878-9293/

(e.g., Davis et al., 2010; Kirschen et al., 2008; Limperopoulos et al., 2007; Limperopoulos et al., 2010; Riva and Giorgi, 2000; Scott et al., 2001; Stoodley and Limperopoulos, 2016; Tavano et al., 2007).

The cerebellum is comprised of two cortex-covered hemispheres and the midline vermis, and can be subdivided into three lobes and ten lobules. The anterior lobe consists of lobules I–V, the posterior lobe includes lobules VI through IX, and lobule X is the flocculonodular lobe. Cerebellar lobules VII and VIII are further subdivided into lobules Crus I, Crus II, and VIIB and lobules VIIIA and VIIIB, respectively. Neuroanatomical and neuroimaging studies have shown that different regions of the cerebellum form closed-loop circuits with specific areas of the cerebral cortex (Middleton and Strick, 1994; Salmi et al., 2010; see Stoodley and Schmahmann, 2010, for review), providing anatomical substrates for cerebellar involvement in both motor control and higher-level cognitive processes. The cerebellar anterior lobe and lobule VIII are interconnected with cortical areas involved in sensorimotor processing, show resting state functional connectivity with these regions, and are engaged during motor tasks; the posterior lobe is connected to non-motor cortical association areas, shows functional connectivity with multiple cortical networks, and is engaged during cognitive and affective processing (Buckner et al., 2011; Khan et al., 2015; O'Reilly et al., 2009; Stoodley and Schmahmann, 2009, 2010; Stoodley et al., 2012). Functional activation patterns reveal both distinct and overlapping cerebellar regions associated with different cognitive tasks (see Stoodley and Schmahmann, 2009; Stoodley, 2012). Converging findings from two meta-analyses of cerebellar functional imaging data (Keren-Happuch et al., 2014; Stoodley and Schmahmann, 2009) report that activation during language paradigms is found in bilateral lobule VI and right lobule VII; working memory tasks engage lobule VII bilaterally and right VIIIA; and cerebellar activation during executive function measures tends to localize to Crus I bilaterally. Reading tasks most often engage right cerebellar lobules VI and VII (see Stoodley, 2015 for review). The right-lateralization of tasks involving verbal information is consistent with the contralateral projections between the right cerebellum and left cerebral cortical areas supporting language processing.

This cerebellar topography is also evident in structural neuroimaging studies in adults, which show that GM in specific regions of the cerebellum correlates with cognitive performance. IQ scores positively correlate with GM volume bilaterally in the posterior cerebellum (Hogan et al., 2011). Language measures have been associated with increased GM in lobules VIIB and VIIIA (Grogan et al., 2009; Richardson and Price, 2009), whereas better reading ability has been associated with increased GM bilaterally in Crus I (He et al., 2013; Kronbichler et al., 2008). Positive correlations between working memory and GM converged in left lobule VI and Crus I (Bernard and Seidler, 2013; Ding et al., 2012). Better executive function performance was associated with greater GM in the medial and right posterior cerebellum (Ridler et al., 2006), and faster processing speed has been linked to increased cerebellar GM bilaterally in left VI and right IV/V (Eckert et al., 2010; Genova et al., 2009). These previous studies provide strong predictions as to the regions of the cerebellum that may support cognitive development in different domains. Further, the majority of structural imaging findings in adults show that increased posterior cerebellar GM is associated with better cognitive performance, suggesting that the mature relationship between cerebellar GM and cognitive scores is in the positive direction.

While cerebellar structure-function relationships have been explored in pediatric clinical populations (see Stoodley and Limperopoulos, 2016 for review), of the handful of studies in healthy children, most have focused more broadly on the relationship between cerebellar GM and IQ rather than subdomains of cognition (Frangou et al., 2004; Pangelinan et al., 2011). One exception may be in the literature on the neural bases of reading development, in which the relationship between cerebellar GM and reading has been investigated in the context of cerebellar grey matter differences in developmental dyslexia (see Stoodley, 2014, 2015 for reviews). Cerebellar structural and functional differences are well-documented in developmental dyslexia (see Stoodley, 2015 for recent review), and differences in cerebellar grey matter in dyslexia converge in bilateral cerebellar lobule VI (e.g., Stoodley, 2014). In pediatric groups including both dyslexic and non-dyslexic readers, GM in bilateral cerebellar lobule VI has been associated with speed of reading (see Kronbichler et al., 2008), and GM in right lobule VII has been associated with pseudoword decoding and passage comprehension (e.g., Eckert et al., 2016). In addition to this work, a recent study of several subdomains of cognition in relation to cerebellar GM is highly relevant to the current study. This study included children and adolescents in the context of a sample spanning a wide age range (12–65 years; Bernard et al., 2015). Significant relationships were reported between GM in posterior cerebellar and vermal regions of interest and working memory, verbal learning, and spatial learning, while GM in anterior/vermal regions correlated with processing speed (Bernard et al., 2015). Unlike previous studies, there was a *negative* relationship between performance and cerebellar GM in these regions (Bernard et al., 2015). The mixed findings in terms of the direction of the association between cerebellar GM and cognitive scores over a large age range suggest potential differences in the developmental trajectory of this relationship.

That said, relatively few studies have examined age as a moderator of the relationship between brain structure and cognition (for exceptions see Bernard et al., 2015; Ducharme et al., 2012; Salthouse, 2011; Schnack et al., 2015; Shaw et al., 2006; Wilke et al., 2003), even though this approach can provide a better understanding of whether the relationships between GM and cognitive domains are stable or change across development. Similar to the cerebral cortex, cerebellar GM volume shows an inverted U-shaped pattern over age, where GM volume increases over time until approximately 11 years of age, after which it begins to decline (Brain Development Cooperative Group, 2012). Voxel-level analyses indicate that different regions of the cerebellum show different developmental trajectories, with the inferior posterior lobe peaking earlier than the anterior lobe and the superior posterior lobe (Taki et al., 2013). Given these varying trajectories for different cerebellar regions, we predict that the relationship between these regions and the cognitive functions subserved by them will change throughout childhood and adolescence, reflecting the protracted development of the cerebellar posterior lobes well into adolescence (see Tiemeier et al., 2010). The developmental time course of specific cerebellar regions is similar to that of the cerebral cortical regions that they connect to (Giedd et al., 1999), suggesting that cerebellar and cortical regions that form functional circuits follow similar developmental patterns – consistent with the prediction that specific regions of the cerebellum may be more important than others during cognitive development.

Here we investigated the relationship between cerebellar grey matter and specific domains of cognition in a typically-developing pediatric population, and determined whether this relationship is stable or changes with age. We aimed to answer open questions regarding which cerebellar regions are associated with different cognitive skills across development, with the hypothesis that specific regions of the cerebellum would be differentially related to cognition in a manner consistent with the functional activation patterns during cognitive tasks. Specifically, we predicted that grey matter in right cerebellar lobules VI and VII would be associated with receptive vocabulary scores; scores on single-word reading would show correlations with grey matter in cerebellar lobule VI bilaterally; working memory performance would be associated