



Triple representation of language, working memory, social and emotion processing in the cerebellum: convergent evidence from task and seed-based resting-state fMRI analyses in a single large cohort



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ABSTRACT

Delineation of functional topography is critical to the evolving understanding of the cerebellum's role in a wide range of nervous system functions. We used data from the Human Connectome Project ($n = 787$) to analyze cerebellar fMRI task activation (motor, working memory, language, social and emotion processing) and resting-state functional connectivity calculated from cerebral cortical seeds corresponding to the peak Cohen's d of each task contrast. The combination of exceptional statistical power, activation from both motor and multiple non-motor tasks in the same participants, and convergent resting-state networks in the same participants revealed novel aspects of the functional topography of the human cerebellum. Consistent with prior studies there were two distinct representations of motor activation. Newly revealed were three distinct representations each for working memory, language, social, and emotional task processing that were largely separate for these four cognitive and affective domains. In most cases, the task-based activations and the corresponding resting-network correlations were congruent in identifying the two motor representations and the three non-motor representations that were unique to working memory, language, social cognition, and emotion. The definitive localization and characterization of distinct triple representations for cognition and emotion task processing in the cerebellum opens up new basic science questions as to why there are triple representations (what different functions are enabled by the different representations?) and new clinical questions (what are the differing consequences of lesions to the different representations?).

Introduction

Evidence from anatomical, neuroimaging, clinical and behavioral studies indicates that the cerebellum is engaged not only in motor control but also in cognitive and affective functions (Schmahmann, 1991, 1996, 1997; Middleton and Strick, 1994; Schmahmann and Sherman, 1998; Levisohn et al., 2000; Riva and Giorgi, 2000; Ravizza et al., 2006; Schmahmann et al., 2007; Baillieux et al., 2008; Stoodley and Schmahmann, 2009; Thompson and Steinmetz, 2009; Tedesco et al., 2011; Stoodley et al., 2012; Keren-Happuch et al., 2014; Koziol et al., 2014; Hoche et al., 2018). This paradigm shift in appreciation of the clinical neuroscience of the cerebellum has mandated a fundamental reconceptualization of cerebellar organization at the systems level

(Schmahmann and Pandya, 1997b; Strick et al., 2009; Schmahmann, 2010; Koziol et al., 2014; Mariën et al., 2014; Baumann et al., 2015; Adamaszek et al., 2017).

In the present study, we explored the functional topography of the cerebellum for motor and cognitive functions. This understanding is critical to the Dysmetria of Thought theory and its embedded notion of the Universal Cerebellar Transform. The Dysmetria of Thought theory (Schmahmann, 1991, 1996, 2010; Schmahmann and Sherman, 1998) holds that the cerebellum modulates behavior, maintaining it around a homeostatic baseline appropriate to context. In the same way that cerebellum regulates the rate, force, rhythm and accuracy of movements, so does it regulate the speed, capacity, consistency and appropriateness of mental or cognitive processes. Dysmetria of movement is matched by

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dysmetria of thought, an unpredictability and illogic to social and societal interaction. The overshoot and inability in the motor system to check parameters of movement are equated, in the cognitive realm, with a mismatch between reality and perceived reality, and erratic attempts to correct the errors of thought or behavior. The theory of the Universal Cerebellar Transform (UCT; [Schmahmann, 2000, 2001, 2004](#)) claims that there is a computation unique to the cerebellum because of the essential uniformity of the cerebellar cortical cytoarchitecture ([Voogd and Glickstein, 1998; Ito, 1993](#)), and this UCT is applied to all streams of information to which cerebellum has access ([Schmahmann, 2000, 2001, 2004; Guell et al., 2017](#)). A corollary of the UCT is the notion of universal cerebellar impairment (UCI), i.e., following cerebellar injury, dysfunction manifests as dysmetria: Dysmetria of movement is the cerebellar motor syndrome; Dysmetria of thought and emotion is the cerebellar cognitive affective syndrome ([Schmahmann and Sherman, 1998; Levisohn et al., 2000](#)), the third cornerstone of clinical ataxiology ([Manto and Mariën, 2015](#)). The Dysmetria of Thought theory is predicated on the existence of two contrasting but complementary anatomic realities: cytoarchitectonic uniformity (the basis of the UCT theory), and highly arranged connective topography linking distinct cerebellar regions with distinct sensorimotor, association and paralimbic areas of the cerebral hemispheres ([Schmahmann and Pandya, 1997a,b, 2008; Dum and Strick, 2003](#)).

The existence and understanding of cerebellar functional topography is thus critical to these contrasting, complementary realities – heterogeneous cerebellar and extracerebellar connectivity, and homogeneous cerebellar cortical cytoarchitecture. Deeper understanding of the presence and arrangement of motor and nonmotor cerebellar functional subregions, the goal of this study, is critical to the evolving understanding of the role of the cerebellum and cerebro-cerebellar interactions in health and disease.

Two motor representations have been recognized in the cerebellum since the work of Snider and colleagues ([Snider and Eldred, 1952](#); see also [Dow, 1939; Combs, 1954](#)), one representation in the anterior lobe (lobules IV and V, extending into the rostral aspect of posterior lobe lobule VI) and the other in lobule VIII ([Fig. 1A](#)). [Woolsey, 1952](#) regarded these as primary and secondary motor representations, along the lines of the dual representation of motor systems in the cerebral hemispheres. This finding has been replicated multiple times: through viral tract tracer

studies in monkey in which M1 cerebral cortex injections label cerebellar lobules IV/V/VI and also lobules VIII/VIII ([Kelly and Strick, 2003, Fig. 1B](#)), in structure-function correlation studies in patients with stroke ([Schmahmann et al., 2009; Stoodley et al., 2016](#)), in PET and task based MRI studies in healthy subjects ([Rijntjes et al., 1999; Bushara et al., 2001; Grodd et al., 2001; Takanashi et al., 2003; Thickbroom et al., 2003; Stoodley and Schmahmann, 2009; Buckner et al., 2011; Stoodley et al., 2012; Keren-Happuch et al., 2014](#)), and with resting state functional connectivity MRI ([Habas et al., 2009; Krienen and Buckner, 2009; O'Reilly et al., 2010; Buckner et al., 2011](#)). Review of earlier physiological studies in cat ([Oscarsson, 1965](#); see [Schmahmann, 2007](#)) demonstrating spinal cord input only to these anterior lobe and lobule VIII regions are consistent with these areas being regarded as the motor cerebellum ([Schmahmann, 2004, 2010; Schmahmann et al., 2009; Stoodley et al., 2016](#)).

Knowledge that the cerebellum is engaged in cognition and emotion, and that the anatomical locations of nonmotor cerebellar circuits are different than those for motor circuits emerged first from anatomical tract tracing investigations ([Schmahmann and Pandya, 1989, 1991, 1993, 1995, 1997a,b, 2008; Schmahmann, 1996; Middleton and Strick, 1998; Kelly and Strick, 2003; Strick et al., 2009](#)) supported by clinical observations ([Schmahmann and Sherman, 1998; Levisohn et al., 2000; Schoch et al., 2006; Schmahmann et al., 2009; Tedesco et al., 2011](#)). Task-based fMRI studies demonstrated that a wide range of cognitive functions activate cerebellum, and a meta-analysis of these studies ([Stoodley and Schmahmann, 2009](#)) showed that the cerebellar activations are topographically arranged, an observation supported by a single case of within-individual topography ([Stoodley et al., 2010](#)), a prospective study of nine healthy participants ([Stoodley et al., 2012](#)), and a second meta-analysis ([Keren-Happuch et al., 2014](#)).

Resting-state functional connectivity studies provided additional support for the highly arranged localization within cerebellum of intrinsic connectivity networks subserving different cognitive domains. These studies observed the primary motor representation in the anterior lobe and adjacent lobule VI and the secondary representation in lobule VIII. They also revealed that most of the human cerebellum is not related to cerebral areas involved with sensorimotor processing, but rather is functionally coupled with cerebral association and paralimbic areas. Further, they suggested that there is a triple representation of resting-

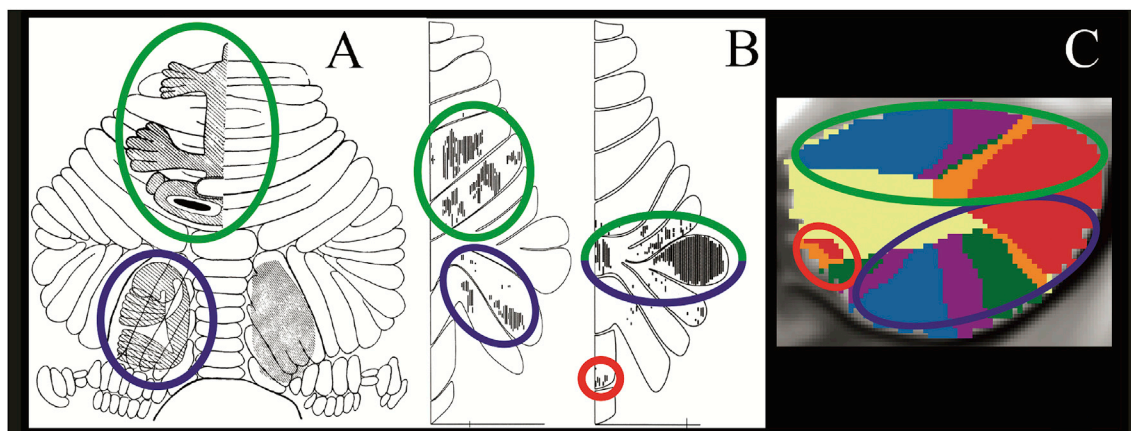


Fig. 1. Convergence of findings from multiple studies of cerebellar topography suggesting an overarching organizing principle based on two motor and three nonmotor representations. Green circles indicate first motor (lobules IV/V/VI) and nonmotor (VI/Crus I) representation; blue circles indicate second motor (lobule VIII) and nonmotor (Crus II/VIII) representation; red circles indicate third nonmotor representation (lobules IX/X). Note that areas of first and second nonmotor representation are contiguous. **A:** Classical electrical stimulation studies showed double representation of sensorimotor activation in the cerebellum (first = lobules IV/V/VI and second = lobule VIII) ([Snider and Eldred, 1952](#); reproduced with permission). **B:** Tract tracing studies demonstrated labeling of the cerebellum in two different locations after injecting viral tracers in motor and nonmotor cerebral cortical areas (viral tracer in M1 labeled cerebellar lobules IV/V/VI and VIII/VIII, left image; viral tracer in prefrontal cortex area 46 labeled cerebellar lobules Crus I/Crus II and IX, right image) ([Kelly and Strick, 2003](#); reproduced with permission). **C:** Resting-state functional connectivity studies suggest that each resting-state network is represented three times in the cerebellum (approximately lobules IV/V/VI/Crus I, lobules Crus II/VIII/VIII and lobules IX/X) with the possible exception of the somatomotor network (represented only twice) (image from [Buckner et al., 2011](#), where each color represents one of the seven resting-state networks defined in [Yeo et al., 2011](#)).

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