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The contributions of cerebro-cerebellar circuitry to executive verbal working memory

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ABSTRACT

Contributions of cerebro-cerebellar function to executive verbal working memory were examined using event-related functional magnetic resonance imaging (fMRI) while 16 subjects completed two versions of the Sternberg task. In both versions subjects were presented with two or six target letters during the encoding phase, which were held in memory during the maintenance phase. A single probe letter was presented during the retrieval phase. In the ‘‘match condition’’, subjects decided whether the probe matched the target letters. In the ‘‘executive condition’’, subjects created a new probe by counting two alphabetical letters forward (e.g., f → h) and decided whether the new probe matched the target letters. Neural activity during the match and executive conditions was compared during each phase of the task. There were four main findings. First, cerebro-cerebellar activity increased as a function of executive load. Second, the dorsal cerebellar dentate co-activated with the supplementary motor area (SMA) during encoding. This likely represented the formation of an articulatory (motor) trajectory. Third, the ventral cerebellar dentate co-activated with anterior prefrontal regions Brodmann Area (BA) 9/46 and the pre-SMA during retrieval. This likely represented the manipulation of information and formation of a response. A functional dissociation between the dorsal ‘‘motor’’ dentate and ‘‘cognitive’’ ventral dentate agrees with neuroanatomical tract tracing studies that have demonstrated separate neural pathways involving each region of the dentate: the dorsal dentate projects to frontal motor areas (including the SMA), and the ventral dentate projects to frontal cognitive areas (including BA 9/46 and the pre-SMA). Finally, activity during the maintenance phase in BA 9, anterior insula, pre-SMA and ventral dentate predicted subsequent accuracy of response to the probe during the retrieval phase. This finding underscored the significant contribution of the pre-SMA/ventral dentate pathway – observed several seconds prior to any motor response to the probe – to executive verbal working memory.

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1. Introduction

Over the past 20 years, neuroimaging has consistently revealed cerebellar activity during cognitive tasks, such as language, working memory, attention, and executive function (for reviews see Ben-Yehudah et al., 2007; Desmond and Fiez, 1998; Desmond and Marvel, 2009). Researchers often did not fully understand these activations given that the cerebellum was traditionally thought to be primarily responsible for motor coordination and balance. As a result, the cerebellum was sometimes used as a control region to compare against activations in other brain regions. Other times, the lower half of the cerebellum was not even included in the scanner's field of view (FOV). Therefore, the contributions of the cerebellum to cognition, for the most part, went undetected.

Clinical data support the notion that cerebellar function extends beyond the motor domain into the cognitive domain. Studies of clinical populations in which the cerebellum is implicated have reported cognitive deficits consistent with reports from the neuroimaging literature (i.e., deficits in language, working memory, and executive function) (Desmond et al., 2003; Desmond and Marvel, 2009; Fiez et al., 1992; Leggio et al., 2000; Nicolson and Fawcett, 2005; Pascual-Leone et al., 1993; Valera et al., 2005). Notably, Schmahmann and Sherman (1997) proposed a cerebellar cognitive affective syndrome based on observations of cognitive and emotional impairments in patients with diseases confined to the cerebellum. They found that these impairments were most clinically prominent in patients with lesions involving the inferior cerebellum (the region of the cerebellum that was often truncated from the FOV during neuroimaging). Children with cerebellar tumor resection have shown verbal working memory deficits that, interestingly, corresponded to the location of the lesion: damage to the left inferior cerebellum was associated with impaired performance when stimuli were delivered in the auditory modality, whereas damage to the right inferior cerebellum was associated with impaired performance when stimuli were delivered in the visual modality (Kirschen et al., 2008). Several other disorders that are said to involve the cerebellum have also been associated with language deficits, such as dyslexia (Nicolson and Fawcett, 2005), attention deficit–hyperactivity disorder (Valera et al., 2005), alcoholism (Desmond et al., 2003), fetal alcohol exposure (O'Hare et al., 2005), and schizophrenia (Marvel et al., 2004).

Neuroanatomical evidence supports a pathway of communication between the cerebellum and the frontal lobe. Retrograde tracers have been used in non-human primates to map regions that project from the cerebellum (Akkal et al., 2007; Dum and Strick, 2003; Hoover and Strick, 1999; Middleton and Strick, 2000, 2001). In such studies, labeled neurons in prefrontal Brodmann's Area (BA) 9 and 46 and the pre-supplementary motor area (pre-SMA), which are considered to be cognitive, traced back to the dentate (Bates and Goldman-Rakic, 1993; Hoshi and Tanji, 2004). Similarly, labeled neurons in the primary motor cortex (M1) and the supplementary motor area (SMA), which are considered to be motor, also traced back to the dentate. Importantly, neurons in BA regions 9/46 and the pre-SMA traced back to ventral portions of the dentate, whereas neurons in the M1 and the SMA traced back to dorsal portions of the dentate. This topographical organization suggests that there are two cerebro-cerebellar pathways – one that supports cognition, and one that supports motor function.

The role of the cerebellum in verbal working memory and executive function has often been studied using variations of the Sternberg paradigm (Sternberg, 1966). In a typical Sternberg task, a subject judges whether a stimulus (probe) is contained in a memorized set of previously presented stimuli (targets). The Sternberg paradigm, therefore, can be divided into three phases: encoding (when targets are presented), maintenance (when target information is rehearsed), and retrieval (when a probe is presented and compared to the encoded targets). Response time (RT) on the Sternberg paradigm is linearly related to verbal working memory load. For example, the greater the number of targets to hold in mind, the longer the RT. Researchers can examine behavior during each phase of the Sternberg task in order to better understand the elements of working memory.

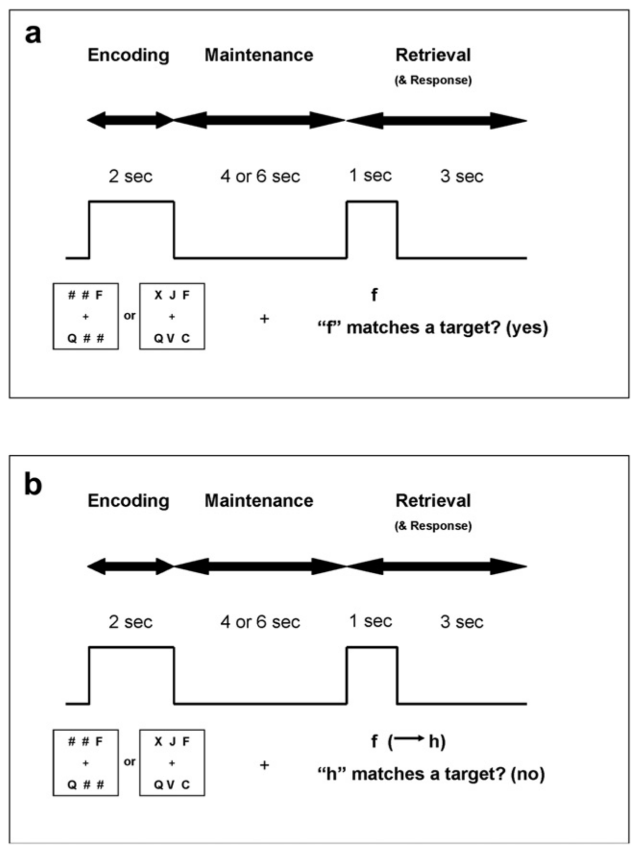

Fig. 1 – Task parameters for the match and executive conditions. Subjects studied two or six targets during the encoding phase and then held those targets in mind during the maintenance phase. a) During the retrieval phase of the match condition, subjects simply decided whether the probe matched any of the targets. b) During the retrieval phase of the executive condition, subjects decided whether two alphabetical letters forward of the probe matched any of the targets. Subjects responded yes/no with a button press.