

## Cerebellar contributions to working memory

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**Anatomical studies show the existence of two well-characterized cortico-cerebellar ‘loops’ that connect prefrontal and cortical motor areas each with their own modules in the cerebellar cortex. The involvement of the cerebellar ‘motor’ modules in motor skills is well established, but little is understood about the way that cerebellar prefrontal modules process information from the prefrontal cortex. This question is particularly important for understanding the *human* cortico-cerebellar system because the prefrontal loop appears to have expanded significantly during the course of evolution. Here, we investigate whether cerebellar modules known to be connected with the prefrontal cortex (specifically within cerebellar cortical lobule VII) become engaged by the execution of skilled cognitive operations. We tested the anatomically specific hypothesis that this area would be activated by the skilled maintenance and manipulation of items within verbal working memory. We used the Paced Auditory Serial Addition Test (PASAT) in combination with a sparse sampling method to avoid artefact caused by speech-related head movement on the BOLD timecourse. Consistent with our hypothesis, we report that activity in the experimental condition was evoked in medial portions of cerebellar cortical lobule VII (relative to a closely matched control task). As would be anticipated, the motor demands common to experimental and control tasks activated face areas of the motor cortex as well as connected motor areas of the cerebellar cortex. We discuss this evidence in the context of theories of cortico-cerebellar information processing.**

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### Introduction

It has been long established that the cerebellum is involved in the control of movement (Holmes, 1939; Glickstein, 1993). This is partly predicated on the finding that in non-human primates, the heaviest projections to the cerebellum arise in the cortical motor system (Brodal, 1978; Glickstein et al., 1985). However, more

recent evidence suggests that cerebellar cortical circuits also process information from areas not directly related to motor control (including areas of the prefrontal cortex; Schmahmann and Pandya, 1997). In particular, such projections are best characterized from Walker’s area 46 (Hoover and Strick, 1999; Kelly and Strick, 2003; Middleton and Strick, 2001; Walker, 1940). The connections of these cortical areas with their cerebellar counterparts form independent modular loops. The motor cortex (area 4) is reciprocally connected with lobules HV, HVI, HVIIB and HVIII of the cerebellar cortex. Prefrontal area 46 (Hoover and Strick, 1999; Kelly and Strick, 2003; Middleton and Strick, 2001) is reciprocally connected to vermal and hemispherical parts of lobule VII. Evidence from diffusion imaging in humans and non-human primates suggests that the prefrontal loop has selectively grown during the course of evolution (Ramnani et al., 2006). While the anatomy of this pathway is now well defined, the processing of prefrontal inputs within connected cerebellar cortical territories is still poorly understood (Ramnani, 2006).

Evidence from neuropsychology has demonstrated that some cerebellar syndromes are associated with cognitive deficits traditionally linked to frontal lobe dysfunction (Drepper et al., 1999; Schmahmann and Sherman, 1998). In particular, some have suggested that cerebellar lesions result in specific impairments in processes related to articulatory planning (Silveri et al., 1998; Zettin et al., 1997). However, it is difficult to draw precise anatomical conclusions on the basis of heterogeneous clinical populations. On the basis of this evidence alone, no inferences about local information processing in the cerebellar cortex can be made because lesions in this location have profound distal effects in connected frontal lobe areas (crossed cortico-cerebellar diaschisis; von Monakow, 1914). In contrast, neuroimaging evidence can investigate information processing in precise anatomical locations, in healthy populations. Such studies have provided clear evidence of cerebellar activity that can be explained purely in terms of cognitive demands (Chen and Desmond, 2005; Desmond et al., 1997, 1998; Desmond and Fiez, 1998; Desmond, 2001).

Recent theoretical accounts of cortico-cerebellar information processing suggest that cerebellar cortical circuits acquire forward models of cerebral cortical information processing that facilitate the automatic execution of those processes, whether in motor or cognitive domains (Ramnani, 2006). The modular organization of

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the cortico-cerebellar system suggests that forward models in each of these domains must be acquired in distinct areas of the cerebellar cortex. Control theoretic accounts suggest that highly practiced execution of actions engage cerebellar circuits (Ito, 2005; Kawato and Wolpert, 1998; Miall and Wolpert, 1996; Wolpert and Kawato, 1998), probably cerebellar components of the motor loop. Similarly, it was predicted that familiar and routine cognitive operations should activate cerebellar cortical components of the prefrontal loop (Ramnani, 2006). Here, we test this hypothesis by manipulating working memory load within a task that requires speech motor control.

The Paced Serial Addition Task (PASAT; Gronwall, 1977) is well known for imposing high cognitive load. This task involves auditory presentation of single digit numbers in pseudo-random order. On presentation of every number ( $n$ ), that number must be added to the preceding number heard in the sequence ( $n-1$ ). Thus, when each number is presented, the previously heard number ( $n-1$ ) must be remembered to complete the addition, but the number preceding that ( $n-2$ ) must be excluded from the calculation (see Fig. 1). This task imposes a number of specific cognitive demands that include the operation of verbal working memory, the phonological loop, speech production, addition and inhibition of cumulative total. Our control task was designed to reduce the cognitive load while holding constant the sensory and motor demands of the task. In comparing the two conditions, we aimed to localize activity evoked by increased cognitive load in the experimental condition (which was over-learned and therefore routine) in relation to the control condition. We predicted that this comparison would reveal activations in the human homologue of macaque prefrontal area 46 (human areas 9/46 of Petrides and Pandya, 1999)—a finding which would be consistent with other reports (Cohen et al., 1997; Curtis and D’Esposito, 2003; Passingham and Sakai, 2004; Schumacher et al., 1996; Smith and Jonides, 1998, 1999). Importantly, we also predicted such activa-

tions in connected cerebellar cortical components of the ‘prefrontal’ loop (lobule VII, including Crus I and Crus II). Only the sensory and motor demands of the task were common to both conditions. Thus, a feature of our analysis strategy was to seek validation of our methods by localizing activity related to both experimental and control conditions (a ‘conjunction’ analysis; Friston et al., 1999). Such activity was expected in the auditory areas of the superior temporal gyrus and the ventral areas of precentral cortex containing representations of orofacial musculature. Furthermore, we predicted that this conjunction would reveal activation of the cerebellar cortical components of the ‘motor’ loop (lobules IV, V and VI).

The requirement to produce an overt verbal response during working memory tasks is relatively demanding compared with other working memory tasks. Hence, our task required the execution of speech movements during fMRI. ‘Sparse sampling’ is commonly employed to overcome the confounding effects of speech-related head motion on MRI data (Abrahams et al., 2003; Amaro et al., 2002; Gracco et al., 2005; Hall et al., 2005). We present a novel variant of this technique in which a period of scanner silence was regularly introduced to enable participants to produce overt verbal response in the absence of EPI scanning. This took advantage of the slow time-constant of the BOLD response, in that it could be sampled after cessation of the motor response. The silent period also allowed us to record and score verbal responses on every stimulus in order to ensure appropriate level of task performance (to our knowledge, other studies employing the PASAT have not used this specific combination of methods).

## Methods

### Participants

15 Right-handed volunteers (aged 18–29; 9 females) participated in the study after giving written and informed consent. They

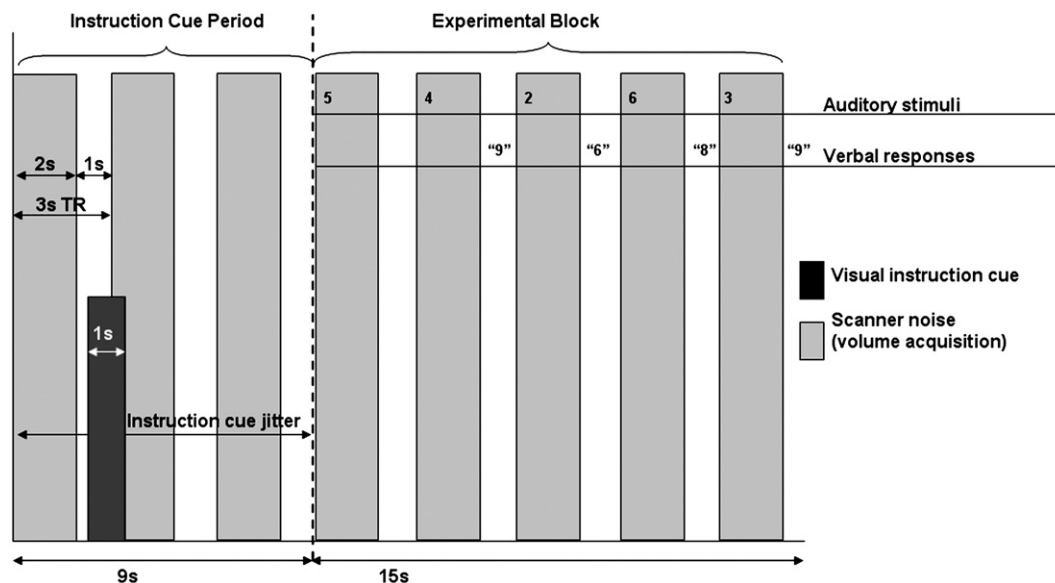


Fig. 1. The instruction cue (specifying the next condition, ADD or REPEAT) was presented for 1 s and was jittered over a 9-s period between the offset of the preceding block and the onset of the following block. 5 Numbers were auditorially presented in each 15-s block, each within the first 1 s of a TR (upper row of numbers). The offset of scanner noise (after the first 2 s of TR onset) served to trigger a verbal response (numbers in speech marks, lower row of numbers). Scanner silence lasted for 1 s.

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