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How the motor system integrates with working memory

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ABSTRACT

Working memory is vital for basic functions in everyday life. During working memory, one holds a finite amount of information in mind until it is no longer required or when resources to maintain this information are depleted. Convergence of neuroimaging data indicates that working memory is supported by the motor system, and in particular, by regions that are involved in motor planning and preparation, in the absence of overt movement. These "secondary motor" regions are physically located between primary motor and non-motor regions, within the frontal lobe, cerebellum, and basal ganglia, creating a functionally organized gradient. The contribution of secondary motor regions to working memory may be to generate internal motor traces that reinforce the representation of information held in mind. The primary aim of this review is to elucidate motor-cognitive interactions through the lens of working memory using the Sternberg paradigm as a model and to suggest origins of the motor-cognitive interface. In addition, we discuss the implications of the motor-cognitive relationship for clinical groups with motor network deficits.

1. Working memory

Working memory is an active process of holding information in mind, which requires allocation of sustained attention (Fougnie, 2008). When attention is diverted, the information held in mind is rapidly replaced by new internal or external inputs. A popular conceptualization of working memory proposed by Alan Baddeley suggests that a central executive system modulates allocation of attentional resources and manages the manipulation of information (Fig. 1A) (Baddeley, 1992). According to Baddeley (1992), the central executive system supervises dual subsystems for holding information in mind: (1) a *phonological loop* for verbal information, and (2) a *visuospatial sketchpad* for visual information (Fig. 1A). Each of these subsystems facilitates passive storage of approximately 1–2 seconds. For maintenance of information beyond the temporal limits of passive storage, active engagement of attention and rehearsal is required (e.g., repeatedly stating the information out loud). The maintenance phase continues long enough to complete the current task or until attention resources are exhausted. The success and duration of active maintenance depends on attention (Fougnie, 2008), stimulus type (e.g., verbal versus nonverbal) and complexity (Luria et al., 2010), and intrinsic working memory capacity of the subject (Miller, 1956).

Baddeley's model is a helpful tool to represent the conceptual components of working memory but is limited when relating these theoretical features to neural mechanisms. Observing neural responses while participants or non-human animals perform short-term memory tasks first established the prefrontal cortex as crucial for working memory, housing neurons that phasically fire to salient events in working memory assessments (Goldman-Rakic, 1996; Miller and Cohen, 2001). For example, non-human primate cell recordings revealed neurons that fired intensely during the delay period (i.e., between the presentation and recall of information) of a working memory task (Funahashi et al., 1990; Fuster and Alexander, 1971; Goldman-Rakic, 1995). Similar delay-sensitive cell populations within the prefrontal cortex have been confirmed in other models, including rats (Yang et al., 2014) and mice (Kamigaki and Dan, 2017). These results in the frontal cortex were accompanied by similar findings across multiple brain regions, including the posterior parietal cortex (Andersen et al., 1987). These results suggested that a broad network was engaged for the short-term maintenance of information (Constantinidis and Procyk, 2004; Goldman-Rakic, 1988).

Cellular recording studies used to identify the link between working memory and neural mechanisms are limited because the recording areas are small (i.e., electrodes record from a handful of neurons or within several millimeters of tissue, a fraction of the entire central nervous system architecture) and the positioning of electrodes is

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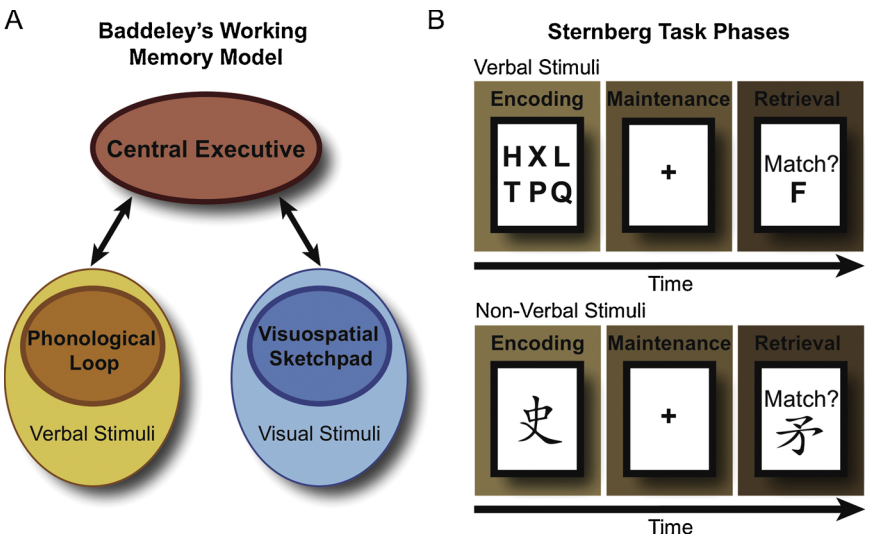

Fig. 1. Baddeley's model of working memory is often tested in the laboratory using the Sternberg Task (Sternberg, 1966). (A) Conceptualization of working memory composed by Baddeley consists of a central executive system that supervises a phonological "loop" and a visuospatial "sketchpad" to hold information in mind over brief periods (e.g., seconds). (B) The Sternberg Task consists of three cognitive phases: (1) encoding of stimuli, (2) maintenance across a delay, and (3) retrieval of the stimuli to compare it with a probe item. The Sternberg task is compatible with both verbal and non-verbal stimuli. Examples shown are derived from Liao et al., 2014.

defined *a priori* by the experimenters. Neuroimaging responds to these challenges of cell recording by measuring changes across large portions of the brain simultaneously and allowing for the assessment of interaction among spatially distant neural networks that otherwise might not be considered integral to the administered task. When a neuroimaging method is coupled with an event-related design, the experimenter can visualize signal changes that represent correlates of neuronal activity in association with particular phases of a function. A common working memory paradigm in human neuroimaging is the Sternberg task (Sternberg, 1966), which uses a delayed item recognition protocol (Fig. 1B). The Sternberg task involves three main phases: (1) encoding, (2) maintenance (delay period), and (3) retrieval. First, novel stimuli (e.g., a letter array) are presented to the participant (encoding phase). The stimuli then disappear, and the participant is instructed to hold the information in mind for several seconds (maintenance phase). During the maintenance phase, the participant is typically prohibited from using an overt behavioral maintenance strategy to record the stimuli, such as speaking aloud. Finally, a probe is presented (e.g., a letter or symbol), and the subject decides if the probe matches one of the originally presented stimuli (retrieval phase). Examining functional magnetic resonance imaging (fMRI) signal changes associated with each phase of the Sternberg task can reveal the necessary functional regions for normal working memory performance, though other working memory paradigms are also commonly used, such as the N-back and paced auditory serial addition test (PASAT).

The consensus among fMRI studies of working memory largely corroborate findings from electrophysiological recordings that reveal the neural mechanisms of working memory to be represented among canonical cognitive structures, including the prefrontal cortex and posterior parietal attention networks (Owen et al., 2005; Pessoa et al., 2002). However, neuroimaging studies of working memory also find neural correlates that were unobserved in the original cellular studies. Motor regions, including the supplementary motor area (SMA), premotor cortex, basal ganglia, and cerebellum are often simultaneously engaged during the maintenance phase of working memory assessments (Wager and Smith, 2003). While clusters of activations in these regions may be reported in a table of statistically significant activations, they are rarely discussed as relevant to working memory performance. Indeed, the signal observed in motor networks could be interpreted as corresponding to the motor preparation and execution components of a behavioral task. Instead, we argue that currently published neuroimaging data support the conclusion that motor networks are highly integrated into working memory processes and are critical for normal performance.

2. Working memory and the motor network

2.1. Defining secondary motor and non-motor regions within the traditional motor network

The development of neuroimaging methodologies in the late 20th century was crucial for revealing the role of cortical motor regions in cognition (Buckner, 2013). Such studies revealed that non-primary motor regions, including the SMA and premotor cortex, were involved in cognitive tasks, including working memory (Awh et al., 1996; Fiez et al., 1996; Paulesu et al., 1993). For the sake of consistency, we will refer to these non-primary motor regions as "secondary" motor regions. Such regions have been shown to activate immediately prior to motor execution (e.g., button press), suggesting a supportive role, such as planning or preparation, but are not directly responsible for overt motor execution (Hulsmann et al., 2003). In the frontal cortex, secondary motor regions are physically situated between the primary motor cortex and cognitive prefrontal cortex, creating a caudal-to-rostral, motor-to-cognitive functional topography (see Fig. 2A). Like the frontal cortex, the subcortical cerebellum and basal ganglia also support both motor function and cognition. We propose that these structures contain secondary motor regions spatially organized along a motor-cognitive gradient.

The cerebellum had traditionally been considered a motor structure, but early neuroimaging studies reinforced ongoing speculation that the cerebellum contributed to non-motor functions (Desmond and Fiez, 1998; Fiez, 1996; Fiez et al., 1996; Petersen et al., 1989; Strick et al., 2009). Evidence suggests that a motor-cognitive functional topography in the cerebellum runs medial to lateral along the coronal plane (Guell et al., 2018b). Cerebellar motor regions include Lobules IV/V with a second motor representation in Lobule VIII, both of which are situated medially, in the anterior and posterior lobes, respectively. Both regions are interconnected to the primary motor cortex (Buckner et al., 2011; Kelly and Strick, 2003). Cognitive regions of the cerebellum include Crus II and Lobule VIIB, which are situated in the lateral aspects of the cerebellar hemispheres and are interconnected to the prefrontal cortex (Kelly and Strick, 2003; O'Reilly et al., 2010; Stoodley and Schmahmann, 2009). Positioned between these motor and cognitive regions are Lobule VI and Crus I, areas that we propose to be "secondary motor" regions that represent the intersection of motor and cognitive cerebellar function (see Fig. 2B). A similar mediolateral topography exists within the second motor representation in Lobule VIII, which can be subdivided into medial VIIIB and lateral VIIIA, partitioned by the intrabiventer fissure (Schmahmann et al., 2000). While VIIIB is directly involved in motor execution (Boillat and van der Zwaag, 2019;

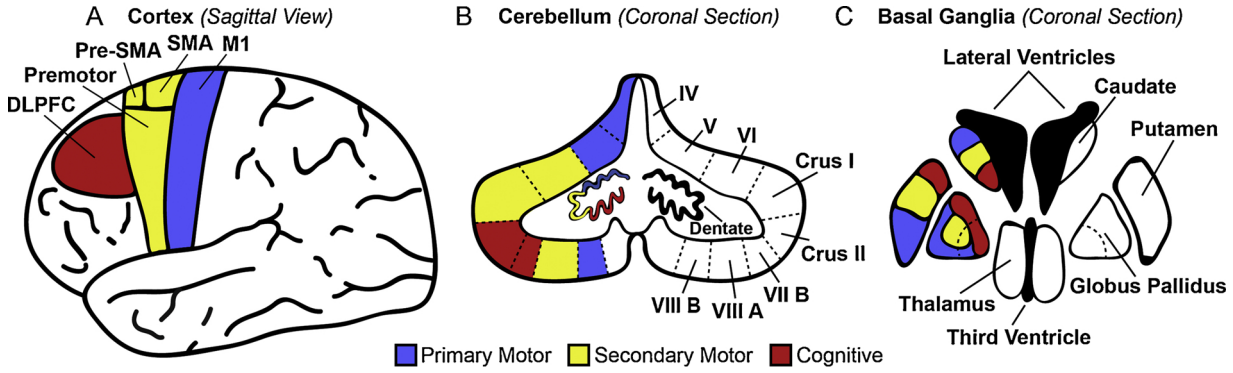

Fig. 2. Functional gradients exist within the frontal lobe, cerebellum, and basal ganglia that range from primarily motor to primarily cognitive. We propose that located within these gradients are "secondary motor" regions that represent the intersection of motor and cognitive functions. Secondary motor regions are typically involved in motor planning and preparation and may support working memory in a similar way by initiating internal motor traces that reinforce the representation of information held in mind. Convergent data across studies indicate that secondary, but not primary, motor areas are active during working memory. (A) In the frontal lobe, a functional gradient runs caudal-to-rostral, beginning with the primary motor cortex (M1), to secondary motor regions of SMA, pre-SMA, and premotor cortex, to the dorsolateral prefrontal cortex (DLPFC). (B) In the cerebellum, a functional gradient includes primary motor, secondary motor, and cognitive regions that extend medial-to-lateral, and is repeated in the superior and inferior regions of the posterior lobe. A separate functional gradient is represented in the dentate nuclei. (C) Within the basal ganglia, each nucleus has its own gradient that is comprised of primary motor, secondary motor, and cognitive functions. DLPFC = dorsolateral prefrontal cortex, SMA = supplementary motor area, M1 = primary motor cortex. Lobule naming in the cerebellum follows the MRI Atlas of the Human Cerebellum by Schmahmann et al., 2000.

Stefanescu et al., 2013; Turesky et al., 2018), Lobule VIIIA has been associated with speech sequence complexity (Bohland and Guenther, 2006), verb generation (Stoodley, 2012; Thurling et al., 2011), and verbal working memory rehearsal (Chen and Desmond, 2005), extending its functions beyond that of primary motor and suggestive of a secondary motor role. Further supporting this notion, human resting state connectivity studies indicate that the primary motor cortex is functionally connected to Lobule VIIIB but not to VIIIA (Buckner et al., 2011; Guell et al., 2018a). Additionally, in the dentate nuclei there is a motor-to-cognitive gradient that runs dorsal to ventral, with a secondary motor region (specifically interconnecting with the SMA) situated in the middle. Taken together, these data suggest there is a topography within the cerebellum that includes regions associated with primary motor, secondary motor, and cognitive functions, organized in a motor-cognitive gradation.

The basal ganglia are a cluster of subcortical nuclei that was once thought to be primarily involved in motor function, but more recently has also become associated with cognition, including working memory (Constantinidis and Procyk, 2004; Leisman and Melillo, 2013). Converging data from human and non-human primate studies indicate the presence of functional gradients within the caudate, putamen, and globus pallidus (GP) separately (see Fig. 2C). In the caudate, the medial/anterior region interconnects with the prefrontal cortex (Draganski et al., 2008; Kelly and Strick, 2004). The lateral/caudal region interconnects with the primary motor cortex (Draganski et al., 2008; Kelly and Strick, 2004). The middle region functionally connects with the premotor cortex and pre-SMA (Draganski et al., 2008; Lehericy et al., 2004), suggesting that a secondary motor region is situated between primary motor and cognitive areas within the caudate. Within the putamen, the medial/anterior region interconnects with the prefrontal cortex, while the lateral/posterior region interconnects with the primary motor cortex (Di Martino et al., 2008; Kelly and Strick, 2004; Lehericy et al., 2004). The middle putamen functionally connects with the SMA, pre-SMA, and premotor cortex (Di Martino et al., 2008; Lehericy et al., 2004), representing a region involved in secondary motor functions. Within the GP, the medial aspect interconnects with the prefrontal cortex (Kelly and Strick, 2004; Middleton and Strick, 2002). The lateral GP interconnects with the primary motor cortex (Hoover and Strick, 1999). As in the other basal ganglia nuclei, a middle region of the GP is interconnected with the SMA (Akkal et al., 2007), creating a secondary motor region located between motor and cognitive regions. Thus, based on interpretations of its connectivity with the frontal cortex, the basal ganglia are broadly organized in a gradient fashion that represents a motor-to-cognitive functional topography.

Collectively, these findings indicate that conventional "motor" structures contain sub-regions that cooperatively participate in motor and cognitive processes. Functions are organized along a motor-cognitive gradation and are determined by local topography and interconnecting brain networks. In this review, we characterize the contributions of the motor network to working memory, with emphasis on the role of secondary motor and non-motor regions within the traditional motor network. Such contributions were evaluated by conducting a review of fMRI event-related working memory studies. By comparing working memory fMRI studies that were similar in methods and analyses, motor networks were consistently found to be active while participants were engaged in working memory rehearsal.

2.2. Literature review: inclusion and exclusion parameters

The Sternberg paradigm enables researchers to directly observe and isolate the neural mechanisms of active rehearsal, which is the core component of working memory. This is possible because during the maintenance phase of the Sternberg paradigm no other stimuli are presented, and no other task demands are required, therefore isolating active rehearsal. In contrast, other working memory tasks elicit processes in addition to rehearsal, such as updating information as new material is continuously presented (e.g., within the N-back or PASAT, etc.). For this reason, this review focuses on findings from studies that have used a Sternberg design. As a result, generalization of findings and interpretations from this review are specific to the Sternberg paradigm and similar behavioral task designs.

Parameters were defined for inclusion related to the participants recruited, task design, stimulus type, and the field of view for data acquisition. Literature to be included in the review was searched in the PubMed (www.ncbi.nlm.nih.gov/pubmed) database of the US National Library of Medicine. The search terms fMRI AND (Sternberg OR item recognition) resulted in 529 hits. Publications were excluded if they: (1) did not involve an event-related design to isolate the maintenance phase activity, (2) did not report whole-brain activity (i.e., cerebral cortex and cerebellum), or (3) involved an overt motor task simultaneous to the working memory assessment, thereby preventing discrimination of motor activity linked specifically to working memory processes. Studies were included when: (1) healthy adult participants

Table 1
Overview of studies that met inclusion criteria for this review. Peaks within Brodmann area 6 outside of SMA (Supplementary Motor Area) were classified as "premotor cortex", and areas within left BA 44 and 45 were classified as "Broca's area." Subpeaks within larger clusters are indicated by indentation.

	Study (N)	Brain Region (Brodmann's Area)	MNI Coordinates			Cluster Size (# voxels)
			x	y	z	
Verbal						
	Bedwell et al., 2005 *(14)*					
		Broca's Area (45)	−58	24	18	3
		Right Caudate	12	20	−5	15
		Left Caudate	−16	17	8	6
		Left Putamen	−20	19	−7	3
	Cairo et al., 2004 (18)					
		Left SMA (6)	−3	16	48	–
		Left Premotor Cortex (6)	−45	−1	55	–
		Left Premotor Cortex (6)	−16	17	59	–
		Right Premotor Cortex (6)	23	16	55	–
		Broca's Area (45)	−50	36	16	–
		Right Cerebellum VI	31	−68	−25	–
	Chang et al., 2007 *(14)*					
		Broca's Area (44)	−56	18	12	3188
		Right Premotor Cortex (6)	30	0	50	218
		Left Putamen	−20	10	−4	–
		Left Caudate	−18	−14	22	–
		Left SMA (6)	0	4	62	1276
		Left Cerebellum VI	−16	−66	−30	229
		Left Cerebellum VI	−8	−78	−18	–
		Left Cerebellum Crus I	−38	−60	−40	113
		Right Cerebellum VI	28	−68	−26	–
	Chein and Fiez, 2001 *(12)*					
		Left Premotor Cortex (6)	−33	−2	43	> 5
		Left Caudate	−14	−3	14	> 5
		Left SMA (6)	1	11	50	> 5
	Chen and Desmond, 2005 *(15)*					
		Broca's Area (44)	−64	12	18	860
		Broca's Area (44)	−56	8	4	–
		Broca's Area (44)	−58	10	24	–
		Left Putamen	−18	10	−11	172
		Right Cerebellum Crus II/VIIb	20	−77	−47	149
	Habeck et al., 2005 (40)					
		Broca's Area (44)	−56	12	3	–
		Left SMA (6)	−5	8	66	–
		Right SMA (6)	8	9	61	–
		Right Premotor Cortex (6)	27	11	58	–
		Left Premotor Cortex (6)	−24	9	57	–
		Right Premotor Cortex (6)	49	8	50	–
	Marvel and Desmond, 2012 *(16)*					
		Left Premotor Cortex (6)	−46	4	40	1160
		Left SMA (6)	−4	8	66	633
		Left SMA (6)	−8	20	52	–
		Right SMA (6)	10	18	52	–
		Left Cerebellum Crus I	−38	−60	−32	228
		Right Cerebellum VI	32	−60	−30	203
		Right Cerebellum VIIb	32	−70	−54	108
	Peterburs et al., 2019 *(20)*					
		Right Cerebellum VIIIa	24	−68	−58	586
		Right Cerebellum VI	24	−66	−18	597
		Left SMA (6)	−2	4	64	787
	Trapp et al., 2014 (16)					
		Broca's Area (44)	−42	5	25	–
		Left Premotor Cortex (6)	−45	−1	46	–
		Left SMA (6)	−3	8	52	–
		Right Cerebellum VI	36	−64	−23	–
		Left Cerebellum Crus II	−30	−64	−41	–
		Broca's Area (44)	−42	5	25	–
	Woodward et al., 2006 (18)					
		Broca's Area (45)	−48	28	32	121
		Left SMA (6)	−4	−12	56	20
		Left SMA (6)	0	24	44	158
		Left Cerebellum Crus II	−32	−68	−40	12
		Right Cerebellum VI	24	−64	−32	203
		Right Cerebellum I-IV	12	−36	−16	17

(*continued on next page*)

Table 1 (*continued*)

Study (N)	Brain Region (Brodmann's Area)	MNI Coordinates			Cluster Size (# voxels)
		x	y	z	
Non-Verbal					
Champod and Petrides, 2007 *(11)*					
	Left SMA (6)	1	6	55	> 110
	Left SMA (6)	−2	−6	60	> 110
	Right Premotor Cortex (6)	33	−6	59	> 110
	Left Premotor Cortex (6)	−54	6	30	> 110
	Left Premotor Cortex (6)	−28	−12	64	> 110
	Left Premotor Cortex (6)	−24	−16	50	> 110
	Left Caudate	−16	−6	19	> 110
	Right Caudate	16	−4	16	> 110
	Left Globus Pallidus	−22	2	3	> 110
	Right Putamen	26	−8	14	> 110
	Right Cerebellum Crus I	35	−58	−30	> 110
	Cerebellar Vermis VI	6	−78	−24	> 110
	Left Cerebellum Crus I	−35	−60	−31	> 110
	Left Cerebellum VIIb	−20	−72	−49	> 110
Pollmann and von Cramon, 2000 (9)					
	Left SMA (6)	−10	10	61	> 100
	Left Premotor Cortex (6)	−50	4	43	> 100
	Right Putamen	19	12	2	> 100
Sobczak-Edmans et al., 2016 (40)					
	Right Premotor Cortex (6)	40	4	58	134
	Right Premotor Cortex (6)	29	7	51	–
	Right Caudate	8	18	9	40
	Left Caudate	−6	18	5	–
	Right Cerebellum Crus I	8	−76	−25	3940
	Cerebellar Vermis VI	−4	−76	−25	–
	Right Cerebellum VI	34	−62	−23	–
	Right Cerebellum VIIb	28	−74	−51	291
	Left Cerebellum VIIb	−30	−74	−51	97

were tested, and (2) the behavioral task design included examination of each of the three Sternberg task phases (encoding, maintenance, and retrieval). To maximize protocol homogeneity among investigations, only studies that visually presented letters, words, pseudo-words, or objects were considered (i.e., paradigms that utilized non-visual stimuli were excluded). A total of 13 neuroimaging studies met these criteria. From these studies, the peak locations of statistically significant clusters during the maintenance phase in primary and secondary motor regions, and cognitive regions within the basal ganglia and cerebellum, were compiled (see Table 1). It is worth noting that "whole brain coverage" may not ensure entire coverage of the cerebellum, particularly the inferior aspect of the posterior lobe (e.g., Lobule VIII). Indeed, one study indicated that the field of view excluded the bottom of the cerebellum in some participants (Chein and Fiez, 2001) and one study indicated the possibility of this happening (Bedwell et al., 2005). Three studies specifically took actions to include all of the cerebellum (Chen and Desmond, 2005; Marvel and Desmond, 2012; Peterburs et al., 2019), while the remaining studies did not specify. This inconsistency represents a limitation in the current results; activity in the inferior cerebellum may, in fact, be more robust than reported here.

2.3. FMRI cluster visualization procedure

Coordinates that were originally reported in space normalized to a Talairach template were converted to Montreal Neurological Institute (MNI) space using the Lancaster transform (Lancaster et al., 2007). Anatomical labels were generated for each cluster peak using Analysis of Functional Neuroimaging (AFNI)'s 'whereami' function (Cox, 1996) according to the area of maximum probability from the Eickhoff-Zilles probabilistic cytoarchitectonic atlas and associated macro labels provided with AFNI 18.2 (Eickhoff et al., 2006, 2007; Eickhoff et al., 2005). Within the cerebellum, labels were based on the region of maximum probability from the Spatially Unbiased Infratentorial (SUIT) atlas (Diedrichsen et al., 2009). There were two peaks reported in the original reports that our methods determined to be in white matter; they were therefore excluded from analyses. Peaks were visualized in the MNI coordinate system, overlaid on surfaces provided by the BrainNet Viewer (Xia et al., 2013).

2.4. Motor activity across working memory neuroimaging studies

The blood-oxygen-level dependent (BOLD) signal clusters overall across the selected neuroimaging studies revealed consistent signal increases among motor-related regions whose activity typically reflects pre-movement processes that occur prior to overt motor execution (Hulsmann et al., 2003), including the pre-SMA, SMA, premotor cortex, and lateral regions of the cerebellum (see Fig. 3 and Table 1). Noticeably absent was activity in the primary motor cortex (lining the anterior side of the central sulcus; see the primary motor cortex border in Fig. 3). This suggests the motor network signal found among these studies did not correspond with overt motor commands and behaviors. A further dissociation was observed such that Broca's area, which is associated with language processing, was specifically activated during the maintenance of verbal information, suggesting that the nature of motor support differed between verbal and non-verbal working memory processes.

These reports suggest that frontal secondary motor regions were recruited during the working memory maintenance phase, in the absence of overt movement and primary motor cortex activation. This functional specificity was replicated in the cerebellum, where lateral parts of the cerebellum were engaged during maintenance, such as Lobule VI, Crus I, and VIIIA, in the absence (with one exception) of activity in primary motor regions within Lobules IV/V and VIIIB. Cognitive cerebellar regions Crus II and 7B were also engaged. Similarly, rehearsal-related activity was observed in the basal ganglia, primarily in the caudate and putamen. It is difficult, however, to determine whether these activations were firmly located in the proposed cognitive and secondary motor sub-regions due to a current lack of defined boundaries for these regions.

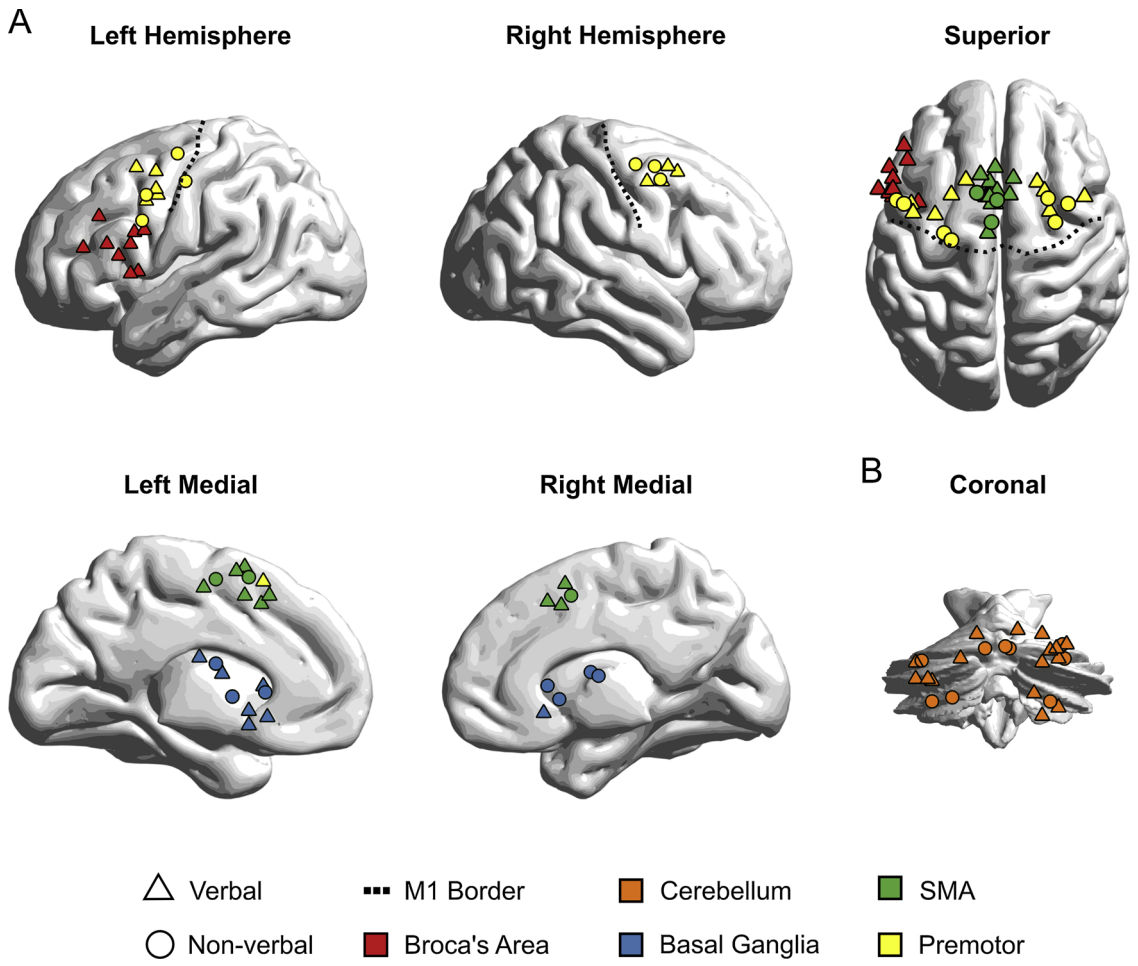

Fig. 3. FMRI signal peak cluster overlay for working memory maintenance across 13 studies, for (A) the cerebrum and (B) the cerebellum. The activations within motor structures revealed consistent overlap within the basal ganglia (blue), supplementary motor area (SMA, green), premotor cortex (yellow), cerebellum (orange) and Broca's area (red). With the exception of Broca's area, these regions are recruited for both verbal (triangles) and non-verbal (circles) stimuli. The dotted line shows the leading anterior edge of primary motor cortex (M1), according to Eickhoff-Zilles cytoarchitectonic atlas (Eickhoff et al., 2006, 2007; Eickhoff et al., 2005), which was used for anatomical labeling. Note that while one peak, due to its position relative to the brain's outer surface, appears posterior to this line in the left hemisphere view, all peaks were classified as anterior of M1. M1 = primary motor cortex, SMA = supplementary motor area.

The findings from the 13 profiled studies correspond to several fMRI studies that demonstrated that activity in secondary motor regions increased with the number of items held in mind (Chein and Fiez, 2001; Chen and Desmond, 2005; Kirschen et al., 2005; Marvel and Desmond, 2010a) and with stimulus complexity, such as when stimuli were unfamiliar (e.g., pseudowords), shared phonological similarity, or involved a manipulation (e.g., re-ordering items in sequence) (Champod and Petrides, 2007; Chang et al., 2007; Chein and Fiez, 2001; Marvel and Desmond, 2012). Similarly, increased premotor, SMA, caudate, and secondary motor cerebellar BOLD signal has been associated with increased working memory demands during the "N-back" working memory task, in which subjects were asked to report whether a stimulus had been presented in the preceding trial (lower demand) or presented 2 or 3 trials prior (higher demand) (Callicott et al., 1999; Kuper et al., 2016). These results imply that secondary motor networks may act as a support to working memory performance in the face of elevated cognitive demands.

Additional evidence comes from a verbal working memory fMRI study (Marvel and Desmond, 2012) that compared brain activity during passive storage and active manipulation of letters. During passive storage, participants simply held a target letter in memory. Meanwhile, manipulation required participants to identify the letter that was two alphabetical letters forward of the target letter (e.g., if presented with "a" then two alphabetical letters forward was "c", or if presented with "k" then "m"). Participants were presented with only two letters in both passive and manipulation conditions, which held the quantity of the load constant. However, the mental representation and rehearsal strategies of those letters differed between conditions as a function of passive storage versus active manipulation. Manipulation of the letters, relative to storage, led to increased secondary motor activity. Moreover, accuracy on the test was negatively correlated with activity in the left premotor cortex and bilateral superior cerebellum, even when only correct trials were included in the analysis. This suggested the secondary motor activity increased because participants were challenged in completing the task (which resulted in overall lower accuracy) but in order to succeed, higher activity was required by these brain regions. Thus, intensity of secondary motor activity scaled with working memory *difficulty*. As supported by the current review, these results from Marvel and Desmond (2012) provide insight that the secondary motor system supports working memory performance, serving as a compensatory aid to ongoing cognitive processes and dynamically changing its activity as one struggles to achieve accuracy in the face of high loads or complex stimuli.

These results focused on healthy individuals, but there are implications of a dynamic motor-cognitive link for clinical groups. For example, damage to secondary motor regions, such as Lobules VI and VIIIA of the cerebellum, may play a role in the subsequently observed working memory deficits (Chiricozzi et al., 2008; Cooper et al., 2012; Stoodley et al., 2016). Likewise, SMA lesions have been associated with verbal working memory impairments, with specific difficulties in information manipulation rather than storage (Canas et al., 2018). In

addition, reduced caudate gray matter has been linked to lower working memory performance and reduced caudate activation in adults with attention deficit/hyperactivity disorder (Roman-Urrestarazu et al., 2016).

While we argue that a direct neurophysiological link between non-primary motor function and working memory performance can underlie the deficits observed in these clinical groups, several alternative explanations should be considered. For example, a motor deficit may distract or otherwise impair performance on a working memory task, particularly when a paradigm requires a motor response (Lange et al., 2016). Moreover, disease burden may act as a confounding variable that impairs cognitive performance and amplifies motor network disruption. Finally, it is important to acknowledge that motor impaired clinical groups may exhibit cognitive deficits due to broadly impacted neural networks or loci, as is the case with several subtypes of ataxia. Therefore, behavioral deficits cannot be easily attributed to disruption of any single region or neural pathway.

2.5. Creation of motor traces during working memory

Neuroimaging reveals that secondary motor networks are involved during working memory maintenance and dynamically change in activity level according to task demands. However, these results do not explain what specific advantages these motor networks offer in working memory. One explanation is that these secondary motor regions support working memory at the cellular level by offering a store of neuronal territory that could be additionally recruited to strengthen signal-to-noise. The recruitment of neurons in secondary motor regions could reduce the likelihood of the maintained information being lost or replaced by off-target stimuli. Alternatively, or in addition, motor networks may influence working memory performance by directly modulating behavior or expanding the number of available rehearsal strategies. There is evidence to support the latter explanation through the creation of *motor traces*.

Motor traces, in this context, are imagined motor representations of salient external or internal information in the absence of overt locomotion (Leisman et al., 2016). For example, internally repeating verbal content or imagining drawing a shape might act as covert motor rehearsal strategies analogous to overt strategies, such as mouthing words or hand tracing (Liao et al., 2014; Marvel and Desmond, 2010b, 2012). Motor traces may reinforce the internal representation of information by offering a redundant rehearsal strategy that can improve the accuracy and duration of maintenance (Koziol et al., 2014). Motor traces may be distinguished from non-motor representations by their role in rehearsal. For example, if the role is to recreate a motor-related association with the information held in mind (e.g., inner speech, inner drawing), then secondary motor regions would engage, in the absence of overt motor actions. However, if the information cannot readily be created into a motor representation, then other regions may be recruited during rehearsal. For example, in a study of verbal working memory for aurally presented unfamiliar backwards speech sounds, the superior temporal sulcus (STS) was engaged during a silent rehearsal phase (Strand et al., 2008). The authors speculated that the STS assisted with covert rehearsal of the novel sounds, an activation that did not occur when verbal content was presented visually (Buchsbaum et al., 2005). The road ahead for testing a hypothesis of dissociable motor and non-motor traces during working memory would include paradigms that relied on contrasting rehearsal mechanisms (e.g., representation of different stimulus modalities) to reveal and characterize the memory traces that separate brain regions or networks engage during rehearsal.

In the context of a Sternberg paradigm, motor traces may be utilized in the maintenance of content that would be inefficient to represent by visual or acoustic means alone. For example, creating an internal trace of the motor sequences that would be necessary to read aloud visually presented letters—without actually saying them aloud—may strengthen memory retention of those letters more than simple visual representation of the orthographic images or acoustic representation of letter sounds would alone. Similarly, creating an internal trace of the motor sequences involved in drawing non-verbalizable symbols, without overtly drawing them, may prolong memory of that symbol far longer than would visual representation. Unlike non-motor representations, motor traces are generated internally. This enables one to hold the information (verbal or non-verbal) in mind for as long as desired, provided that the motor trace can reliably and accurately be regenerated. Supporting this notion, neuroimaging studies of motor imagery (e.g., mental rotation of objects, imagining motor tasks, etc.) have revealed activations in secondary motor regions that overlap with those that support working memory (Szameitat et al., 2007; Vingerhoets et al., 2002), which suggests that participants in these neuroimaging studies used imagery of motor actions to assist with information maintenance.

The role of motor traces in working memory is further confirmed by a previous study in which transcranial magnetic stimulation (TMS) was applied to the primary motor cortex, temporarily disrupting its function and that of interconnected secondary motor regions, while participants performed a Sternberg-type working memory task (Liao et al., 2014; Sternberg, 1966). Participants were presented with three stimulus types: (1) real words (e.g., *race, event, girl, usual*), (2) pseudowords (e.g., *opev, severim, shing, derson*), and (3) non-verbalizable symbols (Chinese characters presented to non-Mandarin readers) (see Fig. 1B). The authors initially hypothesized that verbal working memory relied on inner speech during active rehearsal, which included the motor speech system. Therefore, they predicted that TMS-induced motor disruption would interfere with verbal working memory at higher loads (difficult to remember pseudowords) but would not impact the lower loads (familiar real words). The authors did not expect to find interference for rehearsal of non-verbalizable symbols because rehearsal in that case would not involve inner speech. Results were consistent with their hypothesis for verbal working memory, demonstrating that motor disruption interfered with rehearsal of pseudowords but not with real words. Counter to their hypothesis, however, motor disruption also interfered with rehearsal of non-verbalizable symbols (Chinese characters). As a control condition, TMS was applied to the visual cortex, which had no effect on working memory performance even though stimuli were presented visually. Thus, working memory disruption was specific to motor system perturbation and was evident in both verbal and non-verbal domains.

Within this same study, post-task surveys were administered to identify participant rehearsal strategies. For verbal working memory, participants reported that they covertly rehearsed words and pseudowords. For non-verbal working memory, participants reported imagining themselves physically recreating the stimuli, such as mentally drawing the symbol. Thus, motor imagery rehearsal strategies were often used to hold non-verbal information in mind. Alternative, less motoric strategies for non-verbal rehearsal were also reported, such as attempting to associate object names to symbols as a mnemonic. Subjects were asked to rate the degree to which they relied on any particular strategy type (verbal or motor). Subjects who reported greater reliance on motor trace strategies experienced more working memory disruption following motor cortex stimulation, while those who relied on non-motor strategies were less affected. Collectively, these data link the motor system to working memory function by demonstrating that perturbations to the motor system can directly interfere with working memory.

Liao and colleagues (2014) argued that the working memory impairments were driven by secondary motor network effects rather than primary motor cortex, due to the absence of overt motor task demands. However, an alternative interpretation suggests a role of the primary motor cortex in working memory function, given that the primary motor cortex was directly targeted by TMS. Indeed, primary motor involvement may play a role in working memory, including low-threshold motor activity (e.g., subtle articulations while rehearsing

verbal content). However, converging evidence emphasizes a unique role of secondary motor networks to working memory. Future investigations are needed to directly test primary versus secondary motor cortex contributions to working memory, carefully controlling task demands that may drive motor network engagement (Durisko and Fiez, 2010).

3. Hypothetical origins of motor-cognitive network links

Considering the interaction between cognitive effort and motor system engagement, as represented in working memory, an additional inquiry speculates on the developmental origins and adaptive purpose behind a cognitive system that is supported by secondary motor network activity. Understanding the origins of the motor-cognitive link may help to illuminate the relationship between cognition and motor networks and suggest predictions that can be tested empirically to explain their respective roles. In addition, the origins of these network links are particularly compelling because of the disparate phylogenetic age of many of these network structures, for example, within the neocortex and cerebellum.

The primary function of any nervous system is to survey a changing environment (sensation) and output a specialized response (motor execution) that aligns with the survival needs of the organism. Indeed, less complex, or evolutionarily early, vertebrates are fundamentally defined by a series of sensory-motor relays, adapted for direct interaction with the environment (Fig. 4, Early Brain) (Cisek and Kalaska, 2010). With the absence of cortex, or a canonical cognitive structure, subcortical networks may have been recruited to engage in cognitive processes (Bostan and Strick, 2018). Later in evolutionary development, cognitive networks became available to execute actions associated with executive function, language, and memory. The order of the emergence of these distinct systems (first, sensory-motor, and, second, cognitive networks), suggests that early cognitive networks may have developed directly from the preexisting sensory-motor neural "hardware" (Fig. 4, Intermediate Brain) (Buckner and Krienen, 2013; Jacob, 1977; Koziol and Lutz, 2013). Indeed, the most parsimonious evolutionary model for neural development includes novel systems developing from preexisting architecture of the well-established sensory-motor networks (Diamond, 2000). According to this developmental narrative, at very early stages in cognitive development, the neural territory for sensory-motor function and cognition broadly overlapped. As the environment demanded more complex cognitive functions, cognitive networks expanded their territory beyond sensory-motor networks and specialized. The consequence of this developmental narrative is present among recently evolved vertebrates, particularly primates, where cognition and motor regions occupy discrete cortical territories (Fig. 4, Developed Brain) (Glasser et al., 2016).

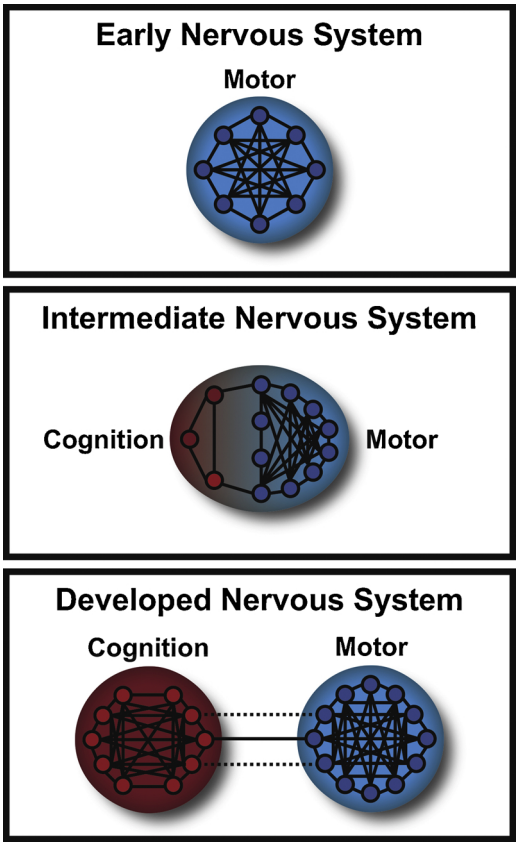

Fig. 4. Evolution of motor-cognitive neural linkage. Early brain consisted of a simple sensory-motor system for basic sensing and behaving to a changing environment. Over time, cognitive regions conferred an evolutionary advantage by facilitating abilities such as memory and executive functions and were built upon existing sensory-motor infrastructure. In the most developed nervous systems (e.g., primates), cognitive and motor regions became specialized and discrete, yet maintained an interdependence.

If the timing of this neural network development narrative is accurate, it is possible that earlier connections between cognitive and motor systems have been preserved in the form of vestigial connectivity. Meanwhile, motor networks that contributed to cognitive performance incurred an evolutionary benefit. For example, holding verbal information in mind over brief delays may have enabled the ability to combine phonemes and attach them to symbolic material, supporting language development (Aboitiz et al., 2006). Evidence for this evolutionary narrative can be found in the anatomy of the primate nervous system. For instance, many pathways bridge motor and cognitive networks, including cortico-cerebellar tracts (Buckner, 2013) and supplementary motor and posterior parietal attention pathways (Blumenfeld, 2002). Function cannot be assumed by the existence of anatomical connections alone. However, functional studies that find connectivity between motor and cognitive structures suggest these anatomical connections, directly or indirectly, carry shared signals (Buckner et al., 2011). Similarly, as described earlier, the cerebellum and basal ganglia are comprised of motor-cognitive functional gradients that suggest a staged addition of network function. In addition, it has been noted that motor and cognitive systems expanded in tandem throughout evolution (Buckner and Krienen, 2013; Diamond, 2000; Dow, 1942). This paired growth is recapitulated in childhood development, during which the prefrontal cortex and posterior-lateral cerebellum are late to reach maturity in early adulthood (Bernard et al., 2016; Diamond, 2000; Tiemeier et al., 2010). In accordance with this well-established structural connection, neuroimaging studies have repeatedly shown that the prefrontal cortex and neocerebellum (the lateral parts of the cerebellum that evolutionarily expanded with the prefrontal cortex) are functionally connected during cognitive tasks, including verbal working memory (Awh et al., 1996; Chen and Desmond, 2005; de Zubicaray et al., 1998; Marvel and Desmond, 2012), attention (Rosenberg et al., 2016), verb generation (Raichle et al., 1994), verbal fluency (Schlosser et al., 1998), and during resting state (Allen et al., 2005; Habas et al., 2009; Krienen and Buckner, 2009; O'Reilly et al., 2010).

In summary, the functional motor-cognitive link may have evolved by building cognitive networks from existing sensory-motor neural architecture, and this development may have been driven by the adaptive advantages of motor-assisted cognition. The resulting architecture is a developed nervous system, as in primates, with examples of both independent and integrated cognitive and motor networks.

4. Clinical implications of motor-cognitive interdependence

Working memory capability varies across individuals (Miller, 1956), which means there is a spectrum of normal ability for the mental

maintenance and manipulation of information. Moreover, it is likely that working memory capacity is dynamic within individuals depending on brain state (Yerkes and Dodson, 1908). According to our model, involvement of the motor system in working memory scales inversely with individual working memory capacity. For example, people with lower working memory capacity recruit motor networks more actively and at lower thresholds of cognitive difficulty than do people with higher working memory capacity. This pattern of motor system behavior during working memory may be compared with the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH) that has been put forth in the field of aging research. CRUNCH proposes that, as people age, their cognitive processing becomes less efficient, resulting in hyperactive neural recruitment at lower working memory loads compared to that of younger adults (Reuter-Lorenz and Lustig, 2005). Hyperactive recruitment of the motor system during working memory has been demonstrated in healthy young adults (Marvel and Desmond, 2012) and by clinical studies when working memory performance was equated between groups, suggesting that clinical populations had to work harder (cognitive effort and/or neural signal amplitude) than healthy controls did to obtain normal working memory performance (Desmond et al., 2003; Forn et al., 2006; Marvel et al., 2012; Reuter-Lorenz et al., 2000; Sweet et al., 2006; Turner and Levine, 2008). However, when working memory performance dropped below that of controls, clinical groups exhibited hypoactivity (Bossong et al., 2012; Mendrek et al., 2004; Mu et al., 2005; Roman-Urrestarazu et al., 2016; Schneider-Garces et al., 2010; Walter et al., 2007). It is unclear whether such hypoactivity is a cause or correlation of the observed low working memory performance. However, it is reasonable to assume that when working memory demands become overwhelmingly difficult, motivation to succeed wanes, along with desire to sustain an effortful strategy. Hence, the rise and fall of neural activity can reflect such working memory constraints (Callicott et al., 1999).

Clinical populations may represent the edge of the spectrum for motor-cognitive interdependence. If working memory is damaged directly (e.g., prefrontal or parietal lesions), this may require greater reliance on the motor system to maintain performance even at intermediate and low memory loads. In addition, we speculate that it may be possible for impairment of motor systems to alter the neural mechanisms of working memory, for example, by limiting motor-based rehearsal strategies, thereby preventing adequate updates in maintenance, or reducing the neuronal territory that would have been recruited for maintenance signaling, thereby reducing signal-to-noise. Motor-cognitive interdependence is an important and under-investigated relationship with clinical implications for cognitive deficits in various movement disorders (e.g., Parkinson's Disease, multiple sclerosis, cerebellar ataxia) and should be rigorously pursued.

Considering clinical observations of people with movement disorders who exhibit cognitive deficits, further research is needed to develop evaluations that specifically test for dual-network interaction deficits, such as the motor and cognitive networks in working memory performance. Current clinical assessments (e.g., Mini-Mental Status Exam) (Folstein et al., 1975) or the Montreal Cognitive Assessment (Nasreddine et al., 2005) may lack the sensitivity to uncover these early and subtle deficits in movement disordered patients. Detecting and treating such cognitive impairments could improve outcomes for these patient populations.

5. Conclusion

A convergence of data from studies utilizing the Sternberg paradigm supports an interaction between motor and cognitive networks in working memory processes. Motor-cognitive interdependence may have originated from motor systems that progressively dedicated neural regions to cognitive demands. The functionality of this interdependence may support an active rehearsal process that serves to lengthen the duration of rehearsal and broaden the type of information that can be held in mind (e.g., non-verbalizable stimuli). This may be accomplished by internally generated motor sequence traces that are actively recreated at will. Disruptions of this motor-cognitive system may contribute to cognitive deficits in a variety of movement disorders. The results and interpretations presented here have been derived from one particular type of working memory paradigm (Sternberg task) and other working memory tasks may reveal less interaction with the secondary motor system. Nonetheless, the cognitive and clinical neuroscience community would benefit from increased attention to motor-cognitive interactions and consideration of the role of motor networks in working memory and other cognitive functions.

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Competing interests

The authors have no competing interests to declare.

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