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Collaboration of Cerebello-Rubral and Cerebello-Striatal Loops in a Motor Preparation Task

Chama Belkhiria[1] · Eya Mssedi[1] · Christophe Habas[2] · Tarak Driss[1] · Giovanni de Marco[1]

Abstract
In this study, we used fMRI to identify brain regions associated with concentration (sustained attention) during a motor preparation task. In comparison with a non-concentration task, increased activities were observed ($P < 0.05$, FWE-corrected P values) in cerebellar lobules VI and VII, motor cortex, pre-supplementary motor area (pre-SMA), thalamus, red nucleus (RN), and caudate nucleus (CN). Moreover, analysis of effective connectivity inter-areal (psychophysiological interactions) showed that during preparation, concentration-related brain activity increase was dependent on *Cerebello-thalamo-pre-SMA-RN* and *Pre-SMA-CN-thalamo-M1* loops. We postulate that, while pre-SMA common to both loops is specifically involved in the movement preparation and readiness for voluntary movement through the striatum, the cerebellar lobule VI in conjunction with RN, likely through a cerebellar-rubro-olivary-cerebellar loop, might be implicated in concentration-related optimization of upcoming motor performances.

Keywords Cerebellum · Red nucleus · Pre-SMA · Caudate nucleus · Motor preparation

Introduction

Motor performances are comprised of several sequential phases such as motor preparation, execution, control, and correction. Several experimental methods [1–3] have demonstrated up to 2 s before voluntary movement onset sequential activations in the anterior cingulate cortex [2], pre-supplementary motor area pre-SMA [4, 5], contralateral sensorimotor cortex, basal ganglia, and thalamus [6]. In particular, pre-SMA plays a pivotal functional role in motor preparation [7]. Pre-SMA is specifically recruited during the early phases of motor (pre) programming of overt and covert (mental preparation), complex, sequential, and externally or internally triggered movements [8]. Pre-SMA would encode spatial organization and temporal ordering of sub-movements, anticipatory postural adjustments, and inhibition of mirror movements [9], while pre-SMA, earlier activated, is implicated in next movement preparation, task switching/inhibition/facilitation and motor learning.

The motor cerebellum is known to be interconnected with motor, lateral and medial premotor (SMA and pre-SMA) areas through cortico-ponto-cerebello-dentato-thalamo-cortical loops [10]. Recent studies also described anatomical cerebello-striatal connections [11]. Cerebellar lobules V–VI and VIII intervene in motor planning, execution, and online correction and learning [12], and the anterior vermis controls postural adjustments [13]. One functional hypothesis suggests that the cerebellum generates an internal model of movements via efferent copy and could compute sensory consequences of the motor command, guiding motor execution [14, 15]. Therefore, it could be postulated that the cerebello-dentato-thalamo-pre-SMA circuit plays an important role in motor preparation, and is particularly affected during motor neuron disease. In line with this hypothesis, patients suffering from, for instance, amyotrophic lateral sclerosis, exhibited beta desynchronization between contra- and ipsilateral motor cortices, increased cerebellar functional connectivity with sensorimotor areas [16], and hyperconnected subcortical motor networks between the basal ganglia and cerebellum [17]. It could be assumed that pre-SMA impairment led to either over-activation of or compensation by alternative cerebello-cortical networks.

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Furthermore, lobules VI and VII take part in the cognitive and limbic cerebellar network, i.e., executive and salience networks, and could take part in the task-related modulation of attention [18, 19]. Being a hub of (pre-) motor, limbic, and cognitive circuits, the cerebellum could monitor and synchronize different motor, limbic, and executive networks recruited by task-complexity and reward-based task. A cognitive role of the red nucleus (RN), probably in relation with salience detection and executive control, was studied in a functional magnetic resonance imaging (fMRI) investigation [20]. The resting state showed that the RN displayed strong functional coherence with associative prefrontal (pre-SMA), insular, temporal, and parietal cortices: the thalamus and the hypothalamus [20]. It has been shown [21] that functional activity of the RN, as well as the lateral cerebellum, is primarily conducted by the sensory processing rather than by motor synchronization, suggesting that the RN may have a key role in the preparation and coordination of voluntary movements.

Previous studies indicated that the sensorimotor network is responsible for programming, executing, and controlling motor function by controlling the primary motor cortex through cerebello-thalamo-cortical connections [22]. The sensorimotor network requires the involvement of cerebellum and basal ganglia, which are functionally and anatomically interconnected. Thalamic output to motor cortex (M1) and SMA has been highlighted, and cerebellar projection to the thalamic nucleus has been mentioned. Although evidence for the role of basal ganglia in cognitive functions is increasing, they have long been associated with premotor processes [23]. Particularly, the caudate nucleus (CN) has been shown to possess an important involvement in motor processes, planning and execution of movement, and goal-directed action [24]. The CN was associated with higher cognitive functions in connection with specific areas such as supplementary motor area, dorsolateral prefrontal cortex, rostral anterior cingulate, and inferior frontal gyri [24]. In a previous study [25], we showed that lobule VI was involved in the motor execution and motivation during verbal encouragement functioning as a motivational and motor integration hub.

Together, this data supports the involvement of the cortico (pre-SMA)-cerebello-thalamo-cortical pathways in motor preparation. In order to provide a more thorough understanding of the neural bases of motor preparation, we propose to model these pathways using an effective connectivity analysis. First, we sought to identify the brain regions associated with greater activity during a preparation task of concentration. Second, we show the existence of a connectivity loop formed by the right cerebellum (lobule VI), thalamus, pre-SMA and RN, given the crucial role that these areas are thought to play in movement preparation. We show that this loop would be influenced by a cognitive cortico-striato-cortical circuit successively encompassing the pre-SMA, caudate nucleus, thalamus, and M1.

Materials and Methods

Subjects

We recruited 22 healthy, young, right-handed volunteers (11 men and 11 women, aged 30.3 ± 4.3 years) who gave their informed consent. The study was conducted according to the guidelines of the Declaration of Helsinki. Exclusion criteria for recruitment in the study were as follows: (i) subjects with a story of stroke or other neurological disorder, (ii) subjects with intensive practice of physical activity, (iii) other causes of significant disability like major medical or physical diseases, and (iv) major psychiatric disorders.

Paradigm

The experiment was performed during a single session and required approximately 1 h per participant. Inside the scanner, subjects received instructions via MR-compatible headphones. They were requested to keep their eyes closed and motionless during the whole experiment. The experimental design was comprised of a familiarization run followed by two runs. Each one of the two experimental runs included five trials. The order of each one was randomized across participants. In a run, participants mentally performed a motor preparation of 6.6 s and were asked to focus (concentrate) on their motor gesture before squeezing the handgrip (concentration task). In the other run, a beep prompted them to squeeze the handgrip as soon as possible; they had to squeeze the handgrip without mental preparation (non-concentration task). Both of the tasks were followed by a long rest period. The details of both tasks are presented in Fig. 1.

Force Signal Measurement

To ensure that participants performed a mental effort of concentration and increased their motivation during the preparation period, we explored the muscle force levels during the execution periods. Force signals were displayed on the computer monitor fixed in the control room. The MRI scanner (General Electric) and Biopac system (Biopac MP150, System Inc., Santa Barbara, CA) simultaneously recorded the functional brain images and force signals. Handgrip force was measured by a pressure transducer (TSD121B-MRI Hand Dynamometer). The handgrip device was an 8-m-long cable, weighed 323 g, and was connected to the Biopac MP150. The metal-free handgrip device was held in the subject's right hand in the MRI room and was connected to the Biopac located in the MRI control room. The force signal was sampled at 200 Hz. The output of the transducer was connected to an amplifier, DA100C, whose output was directed to AcqKnowledge software (Version 4.2, System Inc., Santa Barbara, CA).

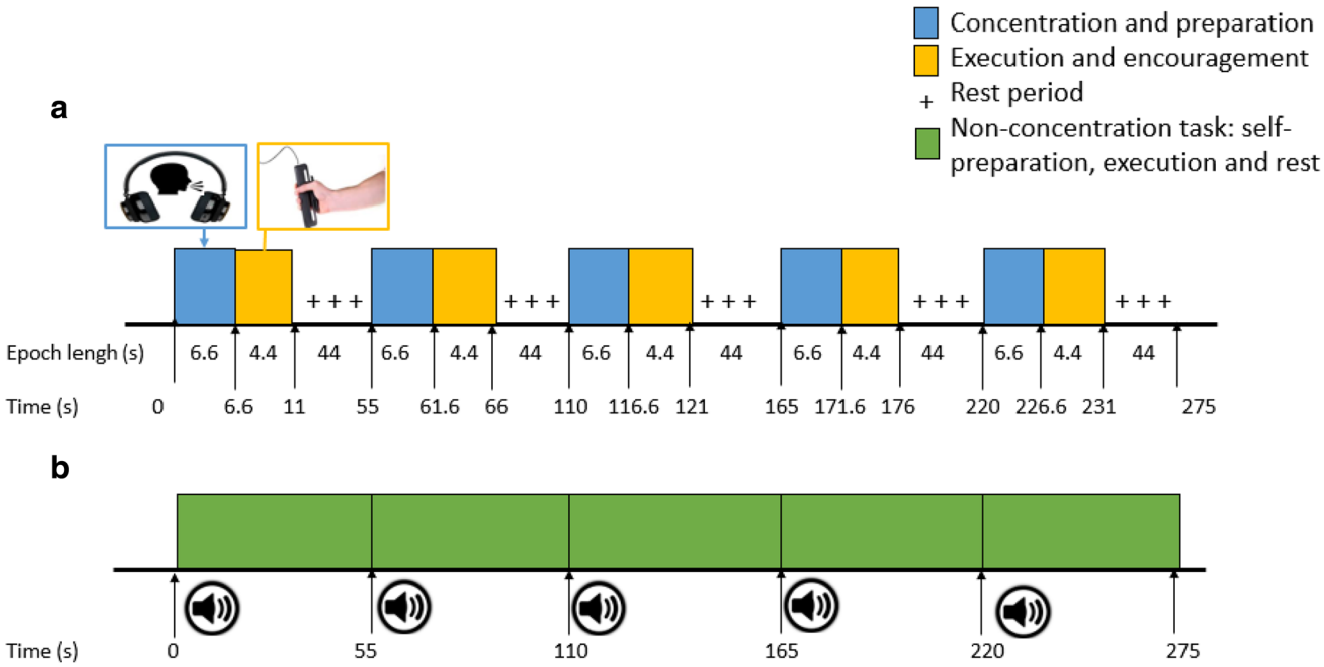


Fig. 1 Schematic timeline of the experiment. **a** Figure showing the concentration task where participants were verbally stimulated (instruction) to prompt concentration (blue, 6.6 s epochs). They were instructed not to move their hand but stay focused on their gesture. Participants were then encouraged during handgrip execution (yellow, 4.4 s epochs), followed by a rest period where participants relaxed (44 s epochs). **b** Diagram of the non-concentration task (green, 55 s epochs), including an auditory beep to signal participants to self-prepare (squeeze the handgrip without focusing on their gesture). All participants used their right hand to complete the two runs of the task. Each run included five trials

fMRI Data Acquisition

A 3-T, whole-body MRI machine, equipped with a head coil (Signa; General Electric Medical System, Milwaukee, WI) was used to acquire functional T2*-weighted images with blood-oxygen-level-dependent (BOLD) contrast, and high-resolution anatomical T1-weighted images. For each subject, functional images consisted of T2* weighted gradient-echo echo-planar (EPI) sequence (TR/TE = 2215/30 ms; flip angle = 80; matrix = 64 × 64; FOV = 240 × 240 mm2; isotropic voxel volume = 52.7 mm3; no interslice gap; 124 volumes/run; two runs per subject). Functional images were co-registered with tridimensional anatomical images obtained with SPGR sequence (matrix, 256× 256; flip angle, 15; TR/TE, 6.608/2.828 ms; 124 slices, 1.2-mm thickness). Head movements were restrained by cushions in order to reduce motion-related artifacts. All MR data was acquired in a single session for each subject.

fMRI Image Pre-processing and Analysis

Functional imaging data and analyses were carried out with Statistical Parametric Mapping software (SPM12, Wellcome Department of Cognitive neurology, UK, implemented in Matlab 2017, MathWorks, Natick, MA). For each subject, functional images were first corrected to adjust for within-volume time differences, then realigned to correct for head motion, co-registered with the anatomical image and smoothed in space using a three-dimensional, 8 mm full width at half maximum Gaussian kernel.

Hemodynamic responses to the preparation task were modeled with a canonical hemodynamic response function (HRF) and its first order temporal derivative. The motion parameters were included in the GLM as regressors to correct the movement. Anatomical masks of the regions were created using the Automated Anatomical Labeling (AAL) Atlas in the SPM Wake Forest University (WFU) PickAtlas toolbox (http:// fmri.wfubmc.edu/software/ PickAtlas, version 2.5) [26].

Group Statistical Parametric Mapping

A single-subject fixed-effect analysis was first performed followed by a random-effects analysis to make inferences to the population. An uncorrected P value 0.005 for the height threshold of each activated voxel was used. While data was acquired in the whole brain, SPM was constrained to specific hypotheses concerning cerebral and cerebellar regions. A priori hypotheses allowed us to restrict statistical analyses to the M1 (-57-10 31), (pre)SMA (-9 22 52), cerebellum (lobule VI) (18 -67 -14), caudate (-18 9 20) and thalamus (-18 -16 16) regions. Results were declared significant for $P < 0.05$ family-wise error (FWE)-corrected for multiple comparison.

Effective Connectivity Analyses

Effective connectivity was assessed using the method of psychophysiological interactions (PPI) [27, 28]. PPI is defined as the change in contribution from one brain area to another due to a change in experimental condition or psychological context [28]. PPI measured the connectivity between defined source and target regions. Four interactions formed the first closed connectivity loop: from lobule VI source region to thalamus to pre-SMA to RN and back to lobule VI. Three interactions formed the second connectivity loop: from pre-SMA source region to caudate to thalamus and then to M1. Extracted hemodynamic time series from each region of interest (seed) were deconvolved and the resulting neuronal time series (physiological variable) were combined with the cue onset times for each stimulus presented under the concentration condition (psychological variables) to derive the interaction term (source signal * experimental context). To test for differences in regression slopes between the two experimental conditions (concentration versus non-concentration), a GLM was generated with this interaction term as the explanatory variable (SPM12 Manual, chapter 36, http://www.fil.ion.ucl.ac.uk/spm/). The resulting individual t-contrast images were entered into a random-effects group analysis and tested for statistical significance at $P < 0.05$ (FWE-corrected).

Results

A significant effect of concentration effort and motivation was found in the force data ($P < 0.05$) between both tasks. Indeed, the mean (± SD) force values during the concentration task were 32.28 ± 13.76 kg while in the non-concentration task it was 26.74 ± 12.36 kg. These results show that subjects improved their force overtime due to their concentration. Taking advantage of the extended motor preparation period in our paradigm, we explored the activated regions related to motor preparation and their associated connectivity.

Table 1 presents the statistical parametric results for the whole brain concerning the contrast "concentration task versus non-concentration task" during the motor preparation task. Table 1 was partitioned in the cerebellar, cortical and subcortical regions, and displays t values obtained with uncorrected $P < 0.005$ values and t values* obtained with FWE-corrected P values ($P < 0.05$).

Brain regions of interest demonstrating significant concentration-specific changes are shown in Fig. 2. The data presents the statistical parametric maps for the regions of interests concerning the contrast "concentration task versus non-concentration task" (FWE-corrected $P < 0.05$) during the motor preparation task. The cerebellum (R lobule VI), left SMA, left motor cortex (M1), left thalamus, and left caudate nucleus were used as seed regions in the psychophysiological interaction analysis.

Figures 3 and 4 illustrate the psychophysiological interaction between the two connectivity loops. Figure 3 shows effective connectivity from the right cerebellar lobule VI source region to the left thalamus to the left pre-SMA target area which was connected to the left RN (FWE-corrected $P = 0.001$).

Figure 4 shows the effective connectivity from the source region (pre-SMA) to the target region (CN). Consistent with anatomical and functional hypotheses, the PPI analysis shows that the left (pre)SMA was significantly (FWE-corrected $P = 0.001$) connected to the left CN, which was significantly (FWE-corrected $P = 0.003$) connected to the left thalamus, which was in turn was significantly connected to the left M1 (FWE-corrected $P = 0.001$).

Discussion

The novelty of this study consists in the demonstration of a significant concentration-related increase of inter-areal effective connectivity between the cerebellar lobule VI, pre-SMA, via thalamus, and RN. These areas may take part, at least, in a (pre-) motor cortico-cerebello-cortical loop, as well as a cerebello-rubro-olivary-cerebellar loop. We discuss below the two loops.

Cerebello-Thalamo-Pre-SMA-RN Loop

It is known that in monkeys, SMA contains force-encoding neurons [29], and ablation of SMA causes disturbed force preparation of grip [30]. In humans, Cramer et al. [31] found a strong correlation between force of squeezing and activation of SMA and S1M1. However, SMA can also play a more general role in initiating (self-paced) movement [6, 32]. Indeed, in fMRI studies, SMA has been shown to be engaged in the early phases of movement preparation, in particular, the progressive elaboration of the spatial and temporal components of the anticipatory postural adjustments (APA). A hypo-activity during gait initiation has been reported within SMA in PD patients with significantly reduced APA magnitude [33], and patients with SMA lesions exhibited an altered timing of the anticipation phase [34]. Another interesting finding concerns the rubral participation within the lobule VI-SMA loop. In humans, the RN receives strong projections from premotor and associative cortex [35] and from contralateral deep cerebellar nuclei, mainly from the dentate nucleus. The RN sends fibers to the bulbar olivary nucleus, through the tegmental central tract, and so takes part in a cerebello-rubro-olivo-cerebellar loop modulated by cortical afferents. ICA-based fcrsMRI [35] has shown integration of the RN in the canonical motor network in humans, whereas seed-based

Table 1 Results of activated regions in concentration task vs. non-concentration task. *BA*, Brodmann areas; MNI (*x*, *y*, *z*) coordinates, *t* values, uncorrected *P* values ($P < 0.005$) and *FWE-corrected *P* values ($P < 0.05$)

Regions	BA	Left side			*t*	Right side			*t*
		MNI coordinates				MNI coordinates			
		x	*y*	*z*		*x*	*y*	*z*	
Cerebellar regions									
Lobule VI		− 15	− 76	− 14	3.54*	18	− 67	− 14	3.65*
Lobule VII		− 45	− 42	− 42	3.32	39	− 63	− 54	3.45
Lobule V		− 15	− 31	− 13	2.73	18	− 53	− 8	2.65
Crus I/II		− 43	− 57	− 29	2.11	39	− 67	− 23	2.45
Brainsteam									
Red nucleus		− 9	− 22	− 2	3.43*	6	− 19	− 11	3.04*
Cortical regions									
Suplementary motor area	6	− 9	22	52	4.35*	9	13	55	3.53*
Pre-suplementary motor area	6	− 2	6	56	3.58*	6	20	44	3.21*
Primary motor cortex	4	− 57	− 10	31	3.52*	63	− 10	28	3.30*
Dorsolateral prefrontal cortex	46	− 39	47	16	2.87	42	44	10	3.39
Orbitofrontal cortex	47	− 33	26	1	2.55	21	32	− 8	2.72
Medial frontal gyrus	9	− 33	23	34	2.22	30	32	37	3.21
Superior frontal gyrus	10	− 3	59	25	2.81	36	35	10	3.14
Inferior parietal lobule	7	− 27	− 69	49	3.16	27	− 58	46	2.83
Sub-cortical regions									
Thalamus		− 18	− 16	16	3.63*	24	− 31	10	3.34*
Caudate		− 18	9	20	3.12*	14	− 14	26	2.87*
Medial globus pallidus		− 12	− 1	− 2	2.45	12	2	− 2	2.67

fcrsMRI also demonstrated broader interconnections especially with associative cortices. In the current study, the effective connectivity analysis showed that RN belongs to the (pre-) motor network. In monkeys, rubral neurons showed activity related to force, speed, direction and amplitude of movements. In cats, rubral activity covaried with the amount of the rate of force change actively produced by the cat [36]. As also shown in our study, the extensive (additional) activation in the RN associated with concentration suggests that the RN may be involved in relaying back to the cerebellum by way of the inferior olive, information associated with cognitive behaviors. Therefore, RN receives movement-related inputs from the cerebellum and from the premotor cortex, likely an efferent copy during the preparation period. According to a forward model hypothesis [37], it can be supposed in our study that the rubro-olivary "couple" might act as a comparator between efferent copy and cerebellar sensory estimation of the planned movement, so as to obtain a squeeze force.

Moreover, motor preparation involves high-level cognitive processes that enable humans to anticipate action, select

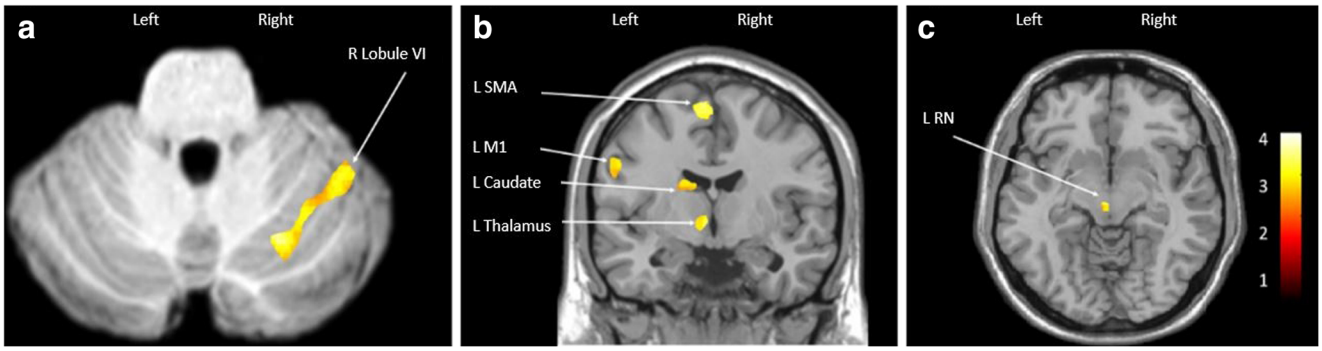


Fig. 2 Statistical parametric map of the average neural activity within the group ($N = 22$) ($P < 0.05$, corrected for multiple comparisons) during the concentration task versus non-concentration task during motor preparation. **a** Axial slice passing through the cerebellum and pons (lobules VI and VII). **b** Coronal slice passing through the encephalon in MNI space (SMA, M1, caudate, thalamus). **c** Axial slice passing through the dorsal red nucleus (RN)

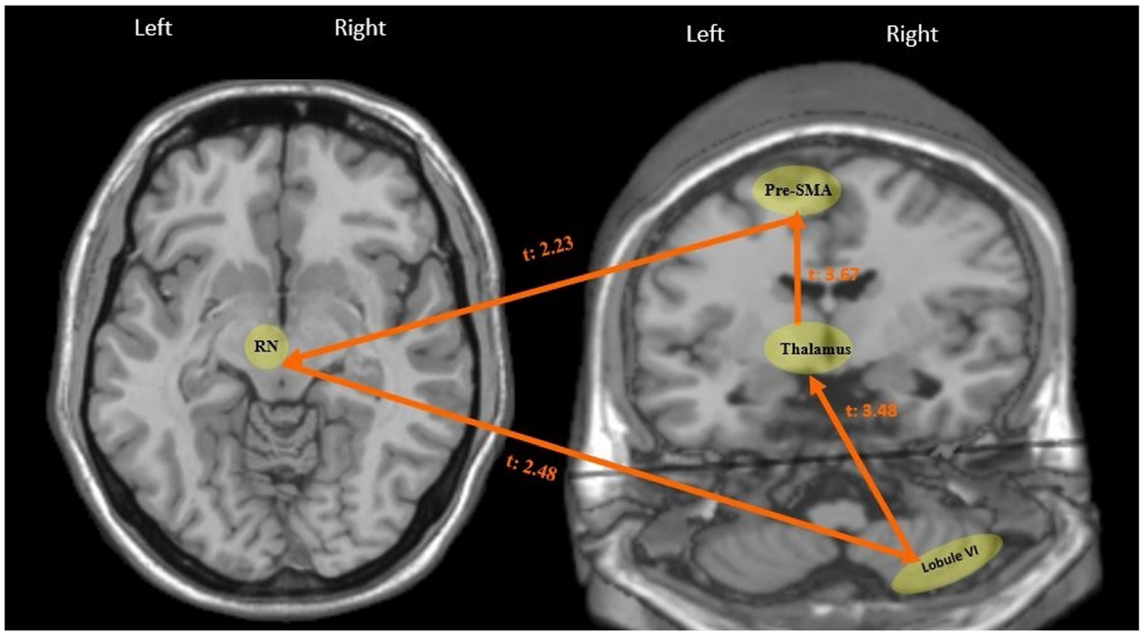


Fig. 3 Effective connectivity of the lobule VI-thalamus-pre-SMA-RN loop. The arrows reflect connectivity from source to target area: from lobule VI (20 -54 -22) to thalamus (-12 -26 8) to SMA (-2 -6 54) to RN (-9 -22 -2). The path coefficients reflect *t* values of the interaction between two regions

responses, decide on movement goals, and control action online [38]. The cerebellum has a crucial role in cognition; in particular, in motor control and movement planning, in the crus I/II and lobule VI. Both areas are implicated in motor control, movement planning, and posture, and are correlated with limb movement [39–41]. Also, it has been shown that the basal ganglia exhibit a preparatory activity and mediate planning and online control processes [38].In particular, the caudate nucleus specifically modulates motor planning processes that are engaged when formulating a plan of action before movement [42]. We have shown a reinforced connectivity between the RN and lobule VI during the concentration-preparation task suggesting that the activity changes in the lobule RN are likely to be principally responsible for programming the activity changes in the lobule VI. Besides the sensorimotor cerebellum, we also recorded, at a liberal statistical threshold (*P* value = 0.005 uncorrected), neocerebellar activations within crus I/II. These neocerebellar regions are interconnected with associative prefrontal (crus I) and parietal cortices (crus II) [18] and participate in executive networks [35]. Consequently, crus I/II could be implied in working memory (task-rule), attention/concentration to the movement preparation and initiation, and to control the internal model processing in conjunction with prefrontal areas BA 9/46, BA 9 10. It could be postulated that the cerebellum and/or the RN could constitute convergent hubs where the motor and associative cerebello-cortical loops could partially overlap and collaborate, since lobule VI is also part of the executive network [18]. It has been shown that lobules VI and VII are recruited together during the very early phase of movement learning in order to improve and automatize the motor performances [19]. The cerebellum might reflect motor commands preparation in

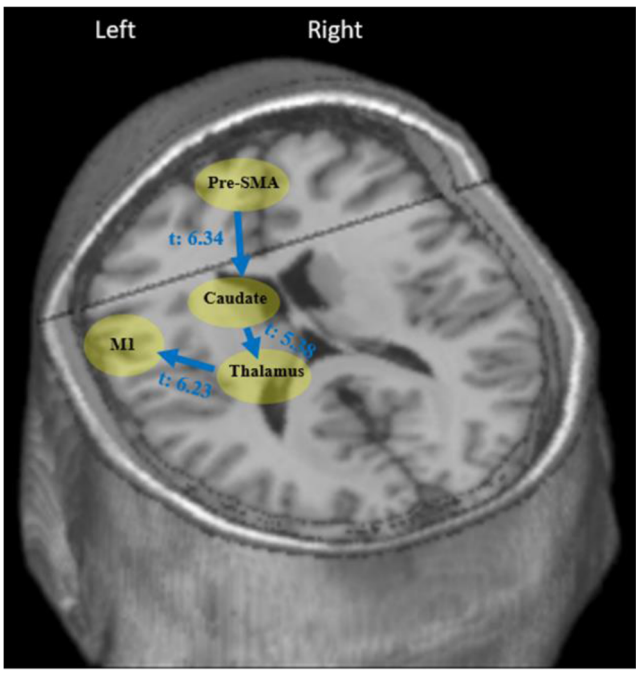


Fig. 4 Effective connectivity of the pre-SMA-caudate-thalamo-M1 circuit. The arrows reflect connectivity from source to target areas: PPI from SMA (-2 -6 54) to caudate (-10 8 4) to thalamus (-12 -26 8) and to M1 (-38 -20 62). The path coefficients reflect *t* values of the interaction between two regions

order to produce the optimal motor behavior for the handgrip to be executed. This hypothesis is supported in our study by a strong connectivity between activity in the pre-SMA, RN and the lobule VI. We do not suggest that lobule VI is the sole generator of premovement activity, but rather that it facilitates the large-scale distributed cortical activity, reflected by effective connectivity, during the preparation of motor task associated with concentration. The lobule VI is positioned as a topographical hub connecting with a wide network of brain regions [25]. Its functionality is thought to be crucial to a broad range of cognitive processes such as attention and motivation [19] and executive processing [43]. In the present context of voluntary movements preparation, the lobule VI is thought to be involved in the process of action initiation. Our results advance knowledge of the crucial involvement of the lobule VI in premotor activity by showing an important contribution of the lobule VI and pre-SMA to the overall increase in cortical activity before movement.

Pre-SMA-CN-Thalamo-M1 Loop

In our study, we were able to identify significant interactions between the pre-SMA-CN, CN-thalamus and thalamus-M1. The role of primary and secondary motor areas in movement preparation has long been explored. The Bereitschaftspotential (readiness), which is measured 800 milliseconds before movement onset, was thought to originate mainly from SMA and M1 [5]. However, the contribution of these areas to motor preparation has been expanded [6]. Here, the described interactions by which the pre-SMA, CN, thalamus and M1 regulate each other's self-feedback connections therefore allow these regions to maintain sustained activity in the presence of concentration. Overall, our findings suggest that the SMA regulates the premotor activity in accordance with premovement neural activity as reflected in the two present loops. Hence, our results are in accordance with previous observations that explored the preparation of motor sequences, finding activations in the fronto-parietal regions [7], DLPFC [7], and basal ganglia [8]. Striatum (including CN) is involved in planning, executing, controlling and learning/automating (skilled) movements, and in reward association learning. Therefore, the CN activation could reflect different intermingled functions. First, the caudate nucleus is involved in high-order processes of movement initiation, such as APA contributing to body posture, accuracy, and speed of movements [44]. CN may be implicated in motor programing by selecting, for instance, appropriate muscles (Juptner), while the cerebellum would pre-initiate dynamical parameters of the movement, using an internal model. In conjunction with pre-SMA, the CN activity may reflect an initiation and anticipation of the motion which precedes the motor execution [45]. The pre-SMA widely projected to the basal ganglia system, which is thought to play a key role in selecting and adapting motor programs based on initial conditions by using proprioceptive input, or in formulating an internal model of body kinesthesia [23].

Likewise, some findings propose an SMA involvement in both classical and "extended" mirror neuron regions during the observation and initiation of movements [46]. The high-order information is thought to be submitted down to the basal ganglia and specifically to the striatum via fronto-striatal loops [47]. Several inputs to the basal ganglia come from the ventral striatum, which receives converging sensory input [48]. More specifically, striatal activity has been linked to action selection and control as well as the mapping of stimuli responses [49–52]. Anatomical evidence shows that the striatal projection neurons are formed by many spines on their dendrites [53], to which glutamatergic cortico-striatal axons make synaptic connection [54]. The CN receives spatial information via the cortico-striatal inputs and rewards related activity through the dopaminergic input [55]. Given the existence of close functional and structural connection between the striatum and the cortex, it has been shown that striatal activation was enhanced by prediction and stimulus preparation [56]. In this context, it seems possible that the CN associated with other cortical structures (e.g., pre-SMA), may be involved in anticipatory or preparatory processes during motor preparation [57, 58].

Conclusion

In summary, the results of this study support the existence of two distinct but collaborative loops during motor preparation: *cerebello-thalamo-pre-SMA-RN and pre*-SMA-*CN*-thalamo-*M*1 loops. Lobule VI participates in the optimization of movement preparation related to the concentration and, thus, could putatively throw a bridge between motor and cognitive circuits. Lobule VI and pre-SMA may constitute hubs facilitating the motor and cognitive integration. RN may be a relay for computation of internal models that are probably coupling between the preparation and the execution phases. Further studies are needed to examine the cognitive effect on motor preparation in patients suffering from SMA or cerebellar dysfunction or attention deficit disorder. The current study gives some additional information about the red nucleus whose function in human remains matter of debate.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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