ELSEVIER

Cognitive Brain Research 8 (1999) 17–25

COGNITIVE BRAIN RESEARCH

Research report

Frontal cortex and the programming of repetitive tapping movements in man: lesion effects and functional neuroimaging

Martin Lepage [a], Gilles Beaudoin [b], Claudine Boulet [a], Irena O'Brien [a], Walter Marcantoni [a], Pierre Bourgouin [b], François Richer [a,*]

[a] *Service de Neurologie, Centre Hospitalier de l'Université de Montréal, Campus Notre-Dame, 1560 Sherbrooke E., Montreal, Quebec, Canada H2L 4M1*

[b] *Service de Radiologie, Centre Hospitalier de l'Université de Montréal, Campus Notre-Dame, 1560 Sherbrooke E., Montreal, Quebec, Canada H2L 4M1*

Accepted 8 December 1998

Abstract

Two studies examined the contribution of human frontal cortical areas to the programming of trains of repetitive movements. The first study compared the performance of patients with unilateral frontal excisions, unilateral temporal excisions and controls on the speed of initiation of discrete vs. sequential tapping movements to visual stimuli. The frontal group showed normal initiation times in single taps and a normal execution (pace and accuracy) in sequential taps but they were slower than the other groups at initiating sequential taps indicating a sequence programming problem for repetitions of a single response. A second study examined the functional anatomy of single and sequential taps in eight control subjects using fMRI. Subjects performed flexion/extension movements of the right thumb at either 1 movement/s or as trains of four closely spaced movements at a rate of 1 train/4 s. Statistical analyses revealed that primary sensorimotor cortex and a dorsolateral premotor cortex region were activated in both conditions. Medial frontal activation was not significant in discrete movements but was clearly present in sequential movements and involved SMA and cingulate regions bilaterally. In addition, two other dorsolateral premotor foci of activation were observed in the sequential taps condition. Results from these two experiments converge toward establishing a significant role of dorsolateral and medial premotor regions in the programming of trains of repetitive responses.

Keywords: Motor programming; Motor control; Sequencing; Tapping; Premotor cortex; fMRI

---

1. Introduction

The precise and rapid execution of complex or sequential movements depends upon both pre-initiation processes involved in planning or programming multiple aspects of the movements and post-initiation processes concerned with response monitoring and correction in addition to final programming. One index of programming processes in sequential responses is initiation time. Initiation time is sensitive to several manipulations of response complexity such as increasing sequence length or movement duration [18,23,40,41,46]. It has also been shown that the timing complexity of response sequences significantly affects initiation time [21,31]. From a neuroscientific perspective, the added initiation time between discrete and sequential responses is an index of the difference in cerebral processing between programming a single response and programming the organization and timing of a response sequence.

A large body of evidence suggests that frontal cortex and especially premotor cortex plays a significant role in the programming processes occurring before the initiation of response sequences. Single-unit studies in monkeys have shown cells exhibiting preparatory activity specific to response sequences in the SMA [50], and in the pre-SMA [45]. Lesions to either medial or lateral premotor cortex in monkeys produce deficits in the production of short sequences of hand movements [15,32,33,37] whereas more anterior lesions seem to have little effect [32]. However, dorsolateral prefrontal lesions can impair the execution of self-generated and externally ordered sequences when stimulus set is increased [34].

In humans, frontal lesions also affect the execution of short response sequences [3,20,26,29,30,47,52]. Qualitative analyses of the sequencing deficits [52] suggest that patients with frontal lesions tend to make selection errors

---

[*] Corresponding author. Fax: +1-514-987-8952; E-mail: richer.francois@uqam.ca

0926-6410/99/$ - see front matter © 1999 Elsevier Science B.V. All rights reserved.
PII: S0926-6410(98)00055-X

such as omitting a response, adding an irrelevant response, or inverting the order of responses. Chronometric approaches have recently been used to investigate these sequencing deficits [16,17,27,28,39]. Frontal lesions increase initiation time and inter-response time in response sequences. They also appear to impair the concurrent programming or selection of multiple responses [27,28]. Richer et al. [39] observed that compared to the other groups, patients with frontal lesions were not significantly slower in single choices but they were slower at making two closely-spaced choice responses and that this slowing did not vary with the separation between the two choices up to 1000 ms. Overall, these observations suggest that an important aspect of the sequential performance deficit is a concurrent programming problem.

A large proportion of studies on the cerebral basis of sequential programming has focused on sequences involving the selection and ordering of multiple responses, also called heterogeneous sequences. However, there is ample evidence that the programming of trains of repetitive movements (homogenous sequences) also requires time. Initiation time increases with the number of finger tapping movements in a series up to about three or four movements [4,13,41,46]. In sequential tapping movements, programming processes are principally concerned with the selection of the correct number of responses in addition to the temporal programming of initiation, pacing and termination of the movement train. If the programming functions of premotor cortex are only concerned with multiple movement selection, these areas should not be critically involved in the programming of sequential tapping movements.

The goal of the present studies was to examine the contribution of frontal cortex to the programming of series of repetitive movements. A first study examined whether frontal lesions produce a deficit in the programming of serial tapping movements. If frontal cortex is involved in the programming of repetitive tapping movements, frontal lesions should exacerbate the effect of sequence length on initiation time or should increase error rate. A second study used fMRI to examine the cortical activation produced in control subjects during the execution of single and repetitive taps.

2. Experiment 1: the effects of frontal lesions on the initiation of tapping sequences

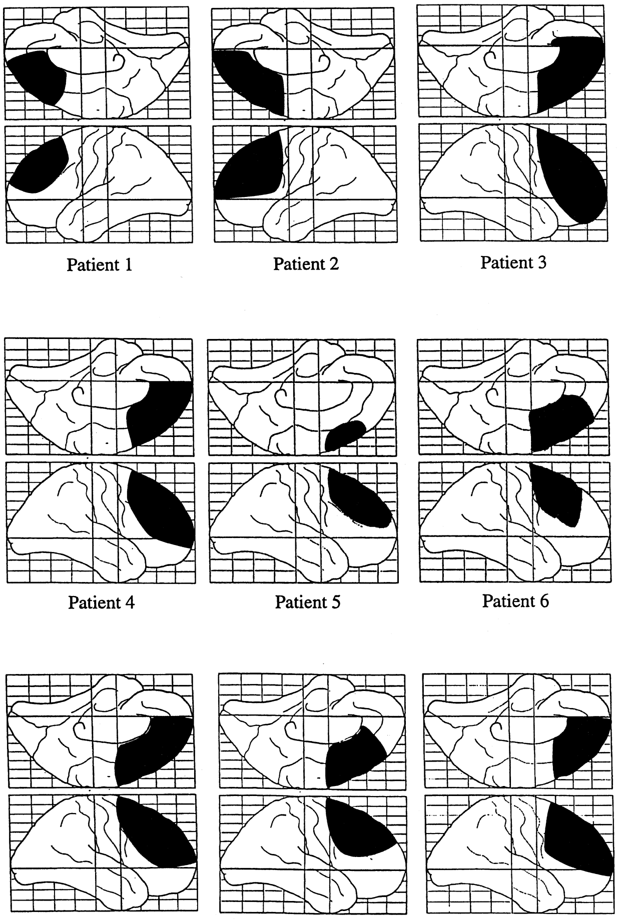
The first study examined whether frontal lobe lesions affect the programming of simple tapping sequences. We compared patients with a frontal lesion to patients with a temporal lesion and control subjects in two tasks requiring keypress movements with the index finger. In a first task, subjects responded with a single keypress to a visual stimulus and in a second task, they executed a series of four closely-spaced keypresses to the stimulus.

2.1. Methods

2.1.1. Subjects

Nine patients with a unilateral frontal excision (seven right, two left) were compared to nine patients with a unilateral temporal excision (five right, four left) and nine controls with no history of cerebral damage. Groups were matched in age (38 years, range 25–51) and education level (10 years, 6–18). Except for one patient with a right frontal glioma (patient #5, Fig. 1), all excisions were performed to alleviate a drug-resistant epilepsy and patients were tested at least 2 years following the surgical intervention. For all subjects, informed consent to participate in the study was obtained according to the rules of the institution.

Fig. 1 shows the extent of the frontal resections. Frontal excisions were variable in extent but always included dorsomedial structures (anterior cingulate gyrus, superior frontal gyrus sometimes including the supplementary motor area) and a variable amount of dorsolateral cortex anterior to the precentral sulcus. Six of the patients with a frontal lesion showed a marked reduction in seizure fre-



Patient 1 Patient 2 Patient 3

Patient 4 Patient 5 Patient 6

Patient 7 Patient 8 Patient 9

Fig. 1. Schematic drawings of the extent of the frontal resections on lateral and medial views of the Talairach grid.

quency after surgery (80% or more), two were seizure-free and all were on anticonvulsant medication. Anterior temporal lobectomies involved resection of the anterior portion of the temporal lobe (about 5 cm from the anterior tip of the lobe), partial resection of the hippocampus, and sparing of Heschl's gyrus. All patients with a temporal lesion showed a marked reduction in seizure frequency (five were seizure-free and four were still on anticonvulsant medication). All patients underwent post-surgery neurological and neuropsychological evaluation. None exhibited sensory or motor impairment or any hemispatial neglect on standard clinical measures. All patients had a WAIS IQ above 80, and all could demonstrate comprehension and retention of task instructions. Neuropsychological evaluation revealed no significant deficits in language, episodic memory, or movement execution. Patients also showed tapping speeds within the normal range in sustained rapid finger tapping.

2.1.2. Tasks and procedure

A computer running Neuroscan software controlled the experiment. All stimuli were presented at the center of the screen against a black background. Each trial began with a fixation cross followed by a white square measuring 2.5 cm × 2.5 cm. Subjects responded to the white square by pressing a button on a keypad as rapidly as possible with the index finger of their dominant hand. Subjects responded with one keypress in the single tap task, and with four closely-spaced keypresses in the repetitive tapping task.

In both tasks, the interval separating the two stimuli was pseudo-random ranging from 500 to 2500 ms in increments of 250 ms and averaging 1500 ms. It has been hypothesized that such random intervals limit the extent to which processes involved in response preparation and response programming can be initiated prior to the imperative stimulus [22]. In the single tap task, subjects performed two blocks of 40 trials preceded by a practice block of 20 trials. In the repetitive tapping task, subjects performed two blocks of 50 trials preceded by a practice block of 20 trials. All subjects first completed the single tapping task followed by the repetitive tapping task. Two-second pauses separated successive trials and a 10-min break separated the two experimental tasks. Initiation time, inter-response intervals and errors were recorded. Only correctly performed sequences were included in the chronometric analysis.

2.2. Results

All groups performed well in both tasks as assessed by the high proportion of correct responses obtained (Table 1). An ANOVA on correct responses revealed a significant effect of task [$F(1,24) = 8.7$, $p < 0.01$], no significant group effect [$F(2,24) = 2.3$, n.s.] and no significant group by task interaction [$F(2,24) = 1.5$, n.s.].

Table 1
Percentage of correct responses in the three groups

	Frontal	Temporal	Control
% Correct responses			
One tap	97.8	98	98.9
	(4.4)	(3.0)	(1.4)
Four taps	86.3	93.3	94.9
	(16.3)	(7.7)	(10.1)

Standard deviations are in parentheses.

Initiation times were analyzed so as to compare the sequence length effect (one tap vs. four taps) in the three groups. Fig. 2 depicts the mean initiation times for the three groups in the single and sequential tapping tasks. The ANOVA on initiation times revealed a significant effect of task [$F(1,24) = 101.7$, $p < 0.0001$], a significant group effect [$F(2,24) = 8.1$, $p < 0.002$] and a significant group by task interaction [$F(2,24) = 12.2$, $p < 0.001$]. Simple effects revealed no significant group differences in single taps (a mean difference of 34 ms between the frontal and the control group, Tukey's HSD, $p = 0.09$, and a mean difference of 26 ms between the frontal and the temporal group, Tukey's HSD $p = 0.24$) but in the sequential tapping task, the frontal group was significantly slower than both the temporal group (mean difference of 112 ms, Tukey's HSD $p < 0.002$) and the control group (mean difference of 121 ms, Tukey's HSD $p < 0.001$).

We also examined group differences in the inter-tap intervals separating the four responses in the repetitive tapping tasks. The ANOVA showed no significant group effect [$F(2,24) = 1.29$, n.s.], no significant effect of response position [$F(2,48) = 0.69$, n.s], and no significant interaction between response position and group [$F(4,48) = 0.74$, n.s.]. Mean inter-tap intervals were: 237 ms (s.d. = 82) in the frontal group, 234 ms (s.d. = 101) in the temporal group, and 187 ms (s.d. = 58) in the control group.

2.3. Discussion

Patients with a frontal lesion showed speeds that were comparable to those of the two control groups when initiating single taps and during the execution of rapid sequences of four taps. However, they were slower than the other two groups at initiating sequences of four taps. These results indicate that frontal lesions affect the programming of repetitive sequential responses and not only sequences involving multiple movement selections. The disproportionate increase in initiation time between one tap and four taps in patients with a frontal lesion indicates that frontal damage affects the programming of trains of repetitive movements in addition to the ordering of multiple distinct movements [27,52]. This suggests that the programming functions of frontal cortex are much more basic

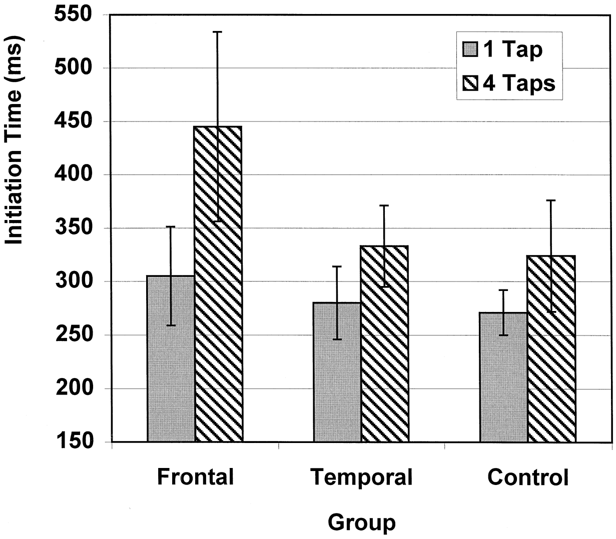


Fig. 2. Mean initiation times in the three groups for single and repetitive tapping tasks. Error bars indicate standard deviations.

than was believed until now. This deficit could only be found with chronometric measures because error measures did not show any deficit in the frontal group.

Patients with frontal lesions showed relatively constant and rapid inter-tap intervals and did not show much difficulty in correctly terminating the repetitive sequences. This lack of execution problems suggests that several parameters of the movement series are correctly programmed before initiation and that the main consequence of unilateral frontal damage is the long duration of these programming processes. This additional programming time probably contributes to the bradykinesia exhibited by these patients. The difficulty may lie in the activation of an adequate representation of the movement sequence, which includes the correct number of individual movements, their pacing and termination. Many models postulate that the construction of such representations is a major determinant of sequence initiation time [43,48,54]. A unilateral frontal lesion may make this activation process longer without preventing it altogether.

It is difficult from our patient sample to determine whether there is a premotor or prefrontal region that is more critical than others for the appearance of this sequential tapping problem since these lesions overlapped extensively from one patient to another. However, only one patient (patient 5) had an excision with little anterior cingulate involvement and he was the only one who showed a normal initiation time in sequential tapping. Patients with anterior cingulate damage but with little premotor damage (patients 1, 4 and 9) showed significant slowing but the maximal slowing was seen in patients (patient 7 and 8) with lesions extending posteriorly to the precentral sulcus and to the anterior commissure line. This preliminary analysis points to the anterior cingulate and the premotor cortex (lateral cortex and pre-SMA) as contributing most to the slowed initiation. However, a contribution of prefrontal regions to the observed sequence initiation deficit cannot be ruled out. In order to examine regional differences in the contribution of frontal regions to the programming of repetitive movement sequences, a second study compared the frontal cortical activation during the execution of discrete and repetitive movements by control subjects.

3. Experiment 2: fMRI activation during single and sequential tapping tasks

Previous functional neuroimaging studies have revealed activations in several frontal cortical regions during motor sequences. Sequences which involve multiple movement selections such as arbitrary thumb to digit opposition movements appear to activate contralateral sensorimotor cortex, as well as dorsolateral premotor cortex and SMA bilaterally [2,5,36,44]. In tasks of continuous flexion/extension of the fingers of the dominant hand, Remy et al. [38] found activation in contralateral sensorimotor cortex and in left SMA using PET, whereas fMRI studies of the same movements have shown activation in contralateral sensorimotor cortex only [36,42]. Boecker et al. [1] reported significant activation of sensorimotor cortex and bilateral activation of the SMA and lateral premotor cortex during self-paced finger tapping. These results suggest that complex or repetitive movements consistently activate sensorimotor cortex but that premotor cortex activation depends on a number of ill-defined parameters. It remains to be investigated whether repetitive tapping movements signalled by external stimuli activate frontal regions anterior to Rolandic cortex.

We examined the frontal cortical activation in simple tapping tasks using fMRI. In a first condition, subjects performed single flexion/extension movements of the right thumb to light flashes presented at a rate of one per second. In a second condition, subjects executed sequences of four rapid thumb movements to light flashes presented at a rate of one every 4 s. Both conditions were identical in terms of the total number of movements in each activation period but differed in the temporal organization of the responses. It was hypothesized that a major difference between single movements and short sequences of repetitive movements would be the activation of premotor cortex.

3.1. Materials and methods

3.1.1. Subjects

Eight right-handed subjects (three males, five females, mean age: 30, range 22–45) with no history of cerebral damage participated in the study. All gave written informed consent to participate according to the rules of the institution.

3.1.2. Tasks and procedure

Subjects lay supine inside the MR scanner and were instructed to maintain their gaze at a fixation cross attached to the ceiling of the scanner. Subjects were scanned during two experimental conditions. In each condition, subjects performed flexion/extension movements of the right thumb signalled by flashes from a stroboscopic light positioned at the feet of the subject. In a pilot study, we found that thumb movements induced significantly less forearm movements than index tapping movements. Each of the two experimental runs consisted of eight cycles of alternating 20-s activation periods and 20-s rest periods. In a first condition, subjects performed discrete thumb movements at a rate of 1/s. In a second condition, they executed sequences of four closely-spaced thumb movements at a rate of 1/4 s (five sequences per activation period). In both conditions, subjects were instructed to respond as fast as possible to the visual stimuli and to complete the sequence of four movements as fast as possible in the sequencing condition. The two conditions were identical in terms of the number of movements executed in each activation period. All subjects performed these two conditions in the order described above. A 4-min pause separated both conditions. All subjects had ample practice with the tasks before the scan.

3.1.3. fMRI method and image analysis

Eighty T_{2*} weighted volume images ($128 \times 128 \times 9$ voxels) were obtained for each of the two experimental conditions using a Siemens Magnetom Vision 1.5T system with echoplanar imaging capabilities. The volumes consisted of nine contiguous transverse sections aligned with the AC–PC line and were acquired every 4 s. Each volume started at the top of the brain and extended to the upper part of the corpus callosum. Voxel dimensions were 1.68×1.68 with a 5-mm slice thickness in a field of view (FOV) of 215 mm. An experimental run consisted of eight cycles of five measures during activation and five measures during rest. Following T_{2*} image acquisition, an arteriovenous volume for the exact same slices was taken (FOV = 215, matrix size = $256 * 128 * 9$) in order to assess the presence of artefactual venous activation foci. The first 10 volumes of each run were excluded from statistical analyses since tissue saturation developed during these acquisitions.

The data were processed and analyzed with statistical parametric mapping SPM96b (developed at the Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks, Sherborn, MA, USA) on a SunSparc 20 workstation [10–12,55]. In each subject, all T_{2*} volumes were realigned to a mean image created from the 10 first volumes of the first run [12], transformed into a standard space [49], then smoothed using an (4 mm FWHM) isotropic Gaussian kernel. Global activity was covaried and a high-pass filter was applied to remove possible confounds of low frequency. In addition, temporal series were smoothed in time. The condition, subject, and covariate effects were estimated according to the linear model at each and every voxel [11]. To test hypotheses about regionally specific condition effects, the estimates were compared using linear contrasts. A delayed box–car curve was used to model hemodynamic changes. The resulting set of voxel values for each contrast constitute a statistical parametric map of the t-statistic (SPM[t]). The SPM[t] were transformed to the unit normal distribution (SPM[Z]) and thresholded at 3.09 ($p = 0.001$ uncorrected).

3.2. Results

Table 2 depicts the cortical frontal activation foci for the two experimental conditions. The highest Z-score within a significant cluster and the corresponding Ta-

Table 2
Foci of activation in frontal areas with the corresponding Talairach coordinates for the discrete and repetitive tapping tasks

Foci of activation	Single taps				Sequences of four taps			
	Z-score	Talairach coordinates			Z-score	Talairach coordinates		
		x	y	z		x	y	z
Left precentral gyrus	7.10	−34	−20	56	7.09	−40	−20	60
Left postcentral gyrus	6.17	−56	−20	54	6.16	−52	−12	44
					3.83	−54	−34	58
Left lateral premotor cortex	4.68	−50	−2	58	5.95	−36	−2	60
					4.95	−30	12	62
					4.80	−46	−2	54
Left medial cortex								
SMA					5.36	−4	−2	68
Ant. Cingulate					6.84	−2	4	46
Right medial cortex								
SMA					6.06	2	2	56
Pre-SMA					4.38	2	8	62
Ant. Cingulate					6.01	2	16	48

The local maxima for each region are represented by the Z-scores and Talairach coordinates are in mm for x, y, z planes.

lairach coordinates are represented for each activation focus. The single tap condition yielded significant activations of primary sensorimotor cortex and dorsolateral premotor cortex contralateral to the moving thumb. Sequences of four taps also induced significant activation in contralateral primary sensorimotor cortex and in dorsolateral premotor cortex. In the latter, two additional dorsolateral premotor cortex foci of activation were observed, one more anterior and one more lateral to the common one. In addition, bilateral medial premotor activation was observed only during repetitive taps. This activation included SMA cortex, extending to the pre-SMA region in the right hemisphere and bilateral regions in the anterior cingulate sulcus. Fig. 3 illustrates brain activations during the single tap and repetitive tapping conditions.

To better characterize the cerebral activation in the two conditions, we performed the same statistical analysis with a much more liberal intensity threshold (2.33, $p = 0.01$, uncorrected). For the sequential tapping condition, this analysis increased the spatial extent of the medial foci of activation but did not reveal any new foci. For the single tap condition, this analysis showed new foci of activation in the medial wall at the level of the cingulate sulcus extending dorsally to the SMA. These results from two different statistical thresholds suggest that the difference in medial premotor activation may be more quantitative than qualitative in nature. Nonetheless, medial premotor regions were clearly more active during repetitive tapping than during single taps.

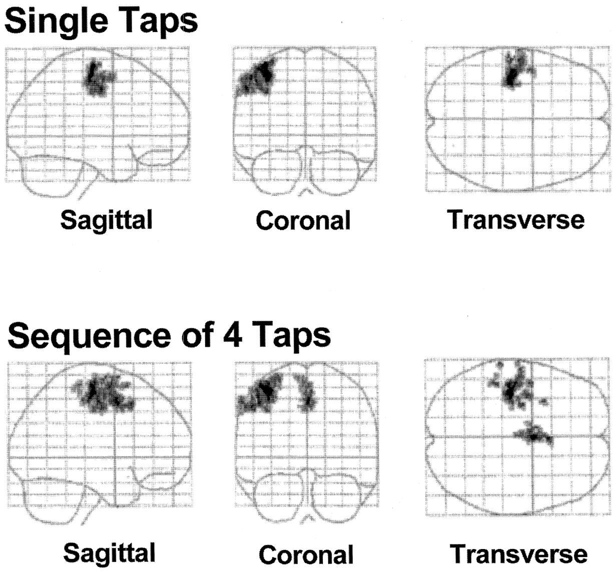


Fig. 3. Orthogonal projections of brain regions showing increased activity ($p < 0.001$, uncorrected) during the simple tap condition (upper panel) and during the repetitive tapping task (bottom panel). The data are represented in a standardized stereotactic space [49]. For single taps, significant activation was observed in left sensorimotor cortex and left dorsolateral premotor cortex. For sequences of four taps, significant activation was observed in left sensorimotor cortex, left dorsolateral premotor cortex, and bilaterally in SMA and anterior cingulate cortex.

3.3. Discussion

Functional neuroimaging of frontal cortical areas during repetitive movements of the thumb revealed differential activations depending on the temporal organization of the responses. Discrete tapping movements at a relatively slow and constant rate induced significant activation in contralateral primary sensorimotor cortex and dorsolateral premotor cortex. When the same movements were temporally organized into short series of closely-spaced movements, they produced additional activation in contralateral dorsolateral premotor regions and in medial premotor regions bilaterally. These results suggest that lateral and medial premotor regions are preferentially activated during repetitive tapping movements. However, repetitive taps contain several features which could contribute to the activation observed. In addition to pre-initiation processing, repetitive taps require post-initiation processing such as sustaining a fast movement rate or the monitoring of response execution so as to correctly terminate the sequence. The relative contribution of pre-initiation and post-initiation processes to premotor cortex activation is still unknown.

Two recent functional neuroimaging studies suggest that activity in premotor regions can be sensitive to the programming complexity of response sequences when execution factors are held constant [2,5]. Both PET studies examined neural activity during the execution of finger sequences and manipulated parametrically sequence length from short sequences of one or four movements to longer sequences of up to 16 movements. Increasing sequence length is known to affect initial programming but also on-line programming of later responses, a process concurrent with the execution of initial responses [18,23,40,46]. In both studies, activity in premotor regions (medial and lateral) was shown to correlate positively with sequence length suggesting that these brain regions are sensitive to programming complexity. This finding rules out the possibility that premotor activity is related to sequence termination since it remained constant across the different sequence length conditions, and suggest instead a role in pre-initiation programming or during concurrent programming. In the present experiment, because sequence length was relatively short and involved a unique repetitive response, it is likely that the major contribution to the premotor activity originated from processes involved in pre-initiation programming. These data along with the fact that frontal lesions do not cause execution problems in sequential tapping converge to suggest that the contribution of premotor cortex is primarily concerned with pre-initiation programming.

4. General discussion

In the first experiment, patients with a frontal lesion showed longer initiation times in sequences of four taps compared to the control groups whereas they showed response speeds comparable to that of both control groups in single taps and in the pace of sequential taps. This effect suggests a contribution of frontal cortex to the programming of repetitive tapping movements. The second experiment showed that both discrete and repetitive tapping movements activated primary sensorimotor cortex and dorsolateral premotor cortex contralateral to the movements whereas additional activation of dorsolateral and medial premotor regions (including SMA and cingulate sulcus) was observed during repetitive taps. These results provide converging evidence of a significant role of dorsolateral and medial premotor regions to the programming of simple repetitive movement series.

4.1. Frontal lobe lesions and motor sequencing deficits

It has long been known that frontal lesions affect the dynamics of sequential movements [14,24,29,30]. The initial clinical descriptions were followed by more detailed studies which have shown that sequencing in patients with frontal lesions is characterized by selection errors such as omissions, intrusions, and ordering errors [3,20,25,26,52]. Studies on the temporal aspects of the frontal sequencing deficit have shown that the problem is exacerbated at higher response rates [20], that it is at least partly attributable to the concurrent programming of temporally adjacent responses [27,28,39], and that the deficit is generalized to the reproduction of tapping rhythms [16].

The programming of repetitive tapping movements may be an instance of the hypothesized timing function of premotor cortex [9]. However, the lack of execution problems in sequential tapping in frontal patients suggests an alternative explanation: that the number of repetitions of the movement is a parameter that is specifically selected or programmed. According to this hypothesis, the incorporation of the number of repetitions into the sequence plan requires activation of premotor regions, a process which takes time and thus affects initiation time. A unilateral lesion in premotor cortex could hamper programming through a mechanism such as interference in neural networks related to response selection [33]. In tapping sequences, this problem would slow the buildup of activation necessary for the completion of programming but execution would not suffer, whereas in heterogenous sequences, response selection errors could also appear.

4.2. Functional neuroimaging of motor sequencing

The fMRI study provided further evidence for a distinction between discrete and repetitive responses in terms of cerebral processing. The observation of additional activations in medial and dorsolateral premotor regions during the sequential taps condition could represent the additional cerebral processing of sequential programming. These findings provide evidence that even simple sequences of a repetitive and invariant movement can activate premotor regions. A number of regions are consistently activated in sequential movements. These include, primary somatosensory cortex [2,5,19,36,38,42], dorsolateral premotor cortex [1,2,5,19,44], anterior cingulate cortex [2,19,44], SMA [1,2,19,36,38,42,44] and to some extent pre-SMA [2,5,6,19]. All these regions were also activated by repetitive movements in the present study. Other regions that did not show activation in the present study have been reported to be involved when sequence complexity is increased. For example, Catalan et al. [5] found that increasing sequence length of finger to thumb opposition sequences yield in addition to regions of the sequence execution network, activations of superior parietal regions bilaterally and of premotor regions ispilateral to the movement. Similarly, Boecker et al. [2] found brain regions correlating with increasing levels of complexity of motor sequences. These regions consisted in the pre-SMA controlateral to the movement, superior parietal regions, and the globus pallidus.

Several studies in animals and man point to the existence of multiple functional areas within medial and lateral premotor cortex. [7,8,33,35,51,53]. In our data, at least three distinct foci of activation appear to be activated by sequential tapping. Patients in the lesion study did not have damage in all these areas. However, all patients showing some slowing did have damage to the anterior cingulate cortex and the slowest patients showed damage in lateral premotor areas and pre-SMA. The relation between the behavioral effects of cerebral lesions and brain activation as revealed by functional neuroimaging techniques (PET, fMRI) is still in its infancy. The observation of a regional activation during task performance does not necessarily imply that it has a critical role in the cerebral implementation of the task. Similarly, a behavioral deficit following a lesion does not automatically imply that the corresponding region will show a significant activation in a PET or fMRI experiment. Issues pertaining to methodological and statistical considerations in functional neuroimaging and of reorganization and adaptation in the lesioned brain will need to be address thoroughly before we can successfully bridge these two fields of research. Nonetheless, in the present experiments, the results suggest a relatively consistent picture across the two experimental approaches in a simple task.

In conclusion, our data suggest that patients with a frontal lesion spend more time programming rapid trains of repetitive movements but can execute fast and accurate response trains once they are programmed. Also, the differential activation between discrete tapping movements and short trains of repetitive movements is consistent with the suggestion that premotor cortex is involved in the differential programming of the two types of movements.

Acknowledgements

This research was supported by the Medical Research Council of Canada, the Fonds de la Recherche en Santé du

Québec and the Savoy Foundation. We thank J.-C. Côté, J. Théberge and R. Habib for computer assistance and the staff of the Magnetic Resonance Unit of Hôpital Notre-Dame for technical assistance. M.L. is now at the Rotman Research Institute of Baycrest Centre, 3560 Bathurst Street, Toronto, Ontario, M6A 2E1.

References

[1] H. Boecker, A. Kleinschmidt, M. Requardt, W. Hänicke, K.D. Merboldt, J. Frahm, Functional cooperativity of human cortical motor areas during self-paced simple finger movements: a high-resolution MRI study, Brain 117 (1994) 1231–1239.

[2] H. Boecker, A. Dagher, A.O. Ceballos-Baumann, R.E. Passingham, M. Samuel, K.J. Friston et al., Role of the human rostral supplementary motor area and the basal ganglia in motor sequence control: investigations with $H_2{}^{15}O$ PET, J. Neurophysiol. 79 (1998) 1070–1080.

[3] A.G.M. Canavan, R.E. Passingham, C.D. Marsden, N. Quinn, M. Wyke, C.E. Polkey, Sequencing ability in parkinsonians, patients with frontal lobe lesions, and patients who have undergone unilateral temporal lobectomies, Neuropsychologia 27 (1989) 787–798.

[4] M.J. Canic, I.M. Franks, Response preparation and latency in patterns of tapping movements, Hum. Mov. Sci. 8 (1989) 123–139.

[5] M.J. Catalan, M. Honda, R.A. Weeks, L.G. Cohen, M. Hallett, The functional neuroanatomy of simple and complex sequential finger movements: a PET study, Brain 121 (1998) 253–264.

[6] M.-P. Deiber, R.E. Passingham, J.G. Colebatch, K.J. Friston, P.D. Nixon, R.S.J. Frackowiack, Cortical areas and the selection of movement: a study with positron emission tomography, Exp. Brain Res. 84 (1991) 393–402.

[7] R.P. Dum, P.L. Strick, The origin of corticospinal projections from the premotor areas in the frontal lobe, J. Neurosci. 11 (1991) 667–689.

[8] G.R. Fink, R.S.J. Frackowiak, U. Pietrzyk, E. Passingham, Multiple nonprimary motor areas in the human cortex, J. Neurophysiol. 77 (1997) 2164–2174.

[9] H.-H. Freund, H. Hummelsheim, Lesions of premotor cortex in man, Brain 108 (1985) 697–733.

[10] K.J. Friston, K.J. Worsley, R.S.J. Frackowiack, J.C. Mazziotta, A.C. Evans, Assessing the significance of focal activations using their spatial extent, Hum. Brain Mapp. 1 (1994) 214–220.

[11] K.J. Friston, A.P. Holmes, K.J. Worsley, J.-B. Poline, C.D. Frith, R.S.J. Frackowiack, Statistical parametric maps in functional imaging: a general linear approach, Hum. Brain Mapp. 2 (1995) 189–210.

[12] K.J. Friston, J. Ashburner, C.D. Frith, J.-B. Poline, J.D. Heather, R.S.J. Frackowiak, Spatial registration and normalisation of images, Hum. Brain Mapp. 2 (1995) 165–189.

[13] A. Garcia-Colera, A. Semjen, The organization of rapid movement sequences as a function of sequence length, Acta Psychol. 66 (1987) 237–250.

[14] K. Goldstein, Mental changes due to frontal lobe damage, Journal of Psychology 17 (1944) 187–208.

[15] U. Halsband, Higher disturbances of movement in monkeys (*Macata mulatta*), in: G.N. Gantchev, B. Dimitev, P.C. Gatev (Eds.), Motor Control, Plenum, New York, 1987, pp. 79–85.

[16] U. Halsband, N. Ito, J. Tanji, H.-J. Freund, The role of premotor cortex and the supplementary motor area in the temporal control of movement in man, Brain 116 (1993) 243–266.

[17] D.L. Harrington, K.Y. Haaland, Motor sequencing with left hemisphere damage, Brain 115 (1992) 857–874.

[18] F.M. Henry, D.E. Rogers, Increased response latency for complicated movements and a 'memory drum' theory of neuromotor reaction, Res. Q. Exerc. Sport 31 (1960) 448–458.

[19] M. Jahanshasi, H. Jenkins, R.G. Brown, C.D. Marsden, R.E. Passingham, D.J. Brooks, Self-initiated versus externally triggered movements: 1. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects, Brain 118 (1995) 913–933.

[20] G.W. Jason, Performance of manual copying tasks after focal cortical lesions, Neuropsychologia 24 (1986) 181–191.

[21] B. Kerr, Task factors that influence selection and preparation for voluntary movements, in: G.E. Stelmach (Ed.), Information Processing, Motor Control and Learning, Academic Press, New York, 1978, pp. 55–69.

[22] S.T. Klapp, Motor response programming during simple and choice reaction time: the role of practice, J. Exp. Psychol.: Hum. Percept. Perform. 21 (1995) 1015–1027.

[23] S.T. Klapp, E.P. Wyatt, W. MacLingo, Response programming in simple and choice reactions, J. Motor Behav. 6 (1974) 263–271.

[24] K. Kleist, Corticale (innervatorische) Apraxie, Jahrbuch für Psychiatrie und Neurologie 28 (1907) 46–112.

[25] B. Kolb, B. Milner, Performance of complex arm and facial movements after focal brain lesions, Neuropsychologia 19 (1981) 491–503.

[26] G. Leonard, B. Milner, L. Jones, Performance on unimanual and bimanual tapping tasks by patients with lesions of the frontal or temporal lobe, Neuropsychologia 26 (1988) 79–91.

[27] M. Lepage, F. Richer, Inter-response interference contributes to the sequencing deficit in frontal lobe lesions, Brain 119 (1996) 1289–1295.

[28] M. Lepage, F. Richer, Quantitative analysis of the sequencing deficits observed after frontal lesions, Soc. Neurosci. Abstr. 22 (1996) 1857.

[29] A.R. Luria, Higher cortical functions in man, Basic Books, New York, 1966.

[30] A.R. Luria, Frontal-lobe syndromes, in: P.J. Vinken, G.W. Bruyn (Eds.), Handbook of Clinical Neurology, Vol. 2, North Holland, Amsterdam, 1969, pp. 725–757.

[31] R.G. Marteniuk, C.L. MacKenzie, Information processing in movement organization and execution, in: R.S. Nickerson (Ed.), Attention and Performance VIII Hillsdale, Lawrence Erlbaum, NJ, 1980, pp. 29–57.

[32] R.E. Passingham, Prefrontal cortex and the sequencing of movement in monkeys (*Macata mulatta*), Neuropsychologia 23 (1985) 453–462.

[33] R.E. Passingham, The Frontal Lobes and Voluntary Action, Oxford University Press, New York, 1993.

[34] M. Petrides, Impairments on nonspatial self-ordered and externally ordered working memory tasks after lesions of the mid-dorsal part of the lateral frontal cortex in the monkey, J. Neurosci. 15 (1995) 359–375.

[35] N. Picard, P.L. Strick, Motor areas of the medial wall—a review of their location and functional activation, Cereb. Cortex 6 (1996) 342–353.

[36] S. Rao, J.R. Binder, P.A. Bandettini, T.A. Hammeke, F.Z. Yetkin et al., Functional magnetic resonance imaging of complex human movements, Neurology 43 (1993) 2311–2318.

[37] G.L. Rea, T.J. Ebner, J.R. Bloedel, Evaluations of combined premotor and supplementary motor cortex lesions on a visually guided arm movement, Brain Res. 418 (1987) 58–67.

[38] P. Remy, M. Zilbovicius, A. Leroy-Willig, A. Syrota, Y. Samson, Movement- and task-related activations of motor cortical areas: a positron emission tomographic study, Ann. Neurol. 36 (1994) 19–26.

[39] F. Richer, S. Bédard, M. Lepage, M.-J. Chouinard, Frontal lesions produce a dual-task deficit in simple rapid choices, Brain Cogn. 37 (1998) 173–175.

[40] D.A. Rosenbaum, V. Hindorff, E.M. Munro, Scheduling and programming of rapid finger sequences: tests and elaborations of the hierarchical editor model, J. Exp. Psychol.: Hum. Percept. Perform. 13 (1987) 193–203.

[41] D.A. Rosenbaum, A.W. Inhoff, A.M. Gordon, Choosing between movement sequences: a hierarchical editor model, J. Exp. Psychol.: Gen. 113 (1984) 372–393.

[42] G. Schlaug, J.N. Sanes, V. Thangaraj, D.G. Darby, L. Jäncke et al., Cerebral activation covaries with movement rate, Neuroreport 7 (1996) 879–883.

[43] A. Semjen, R. Gottsdanker, Rapid serial movements: relation between the planning of sequential structure and effector selection, in: M. Jeannerod (Ed.), Attention and Performance XIII Hillsdale, Lawrence Erlbaum, NJ, 1990, pp. 409–427.

[44] H. Shibasaki, N. Sadato, H. Lyshkow, Y. Yonekura, M. Honda et al., Both primary motor cortex and supplementary motor area play an important role in complex finger movement, Brain 116 (1993) 1387–1398.

[45] K. Shima, H. Mushiake, N. Saito, J. Tanji, Role for cells in the presupplementary motor area in updating motor plans, Proc. Natl. Sci. USA 93 (1996) 8694–8698.

[46] S. Sternberg, S. Monsell, R.L. Knoll, C.E. Wright, The latency and duration of rapid movement sequences: comparisons of speech and typewriting, in: G.E. Stelmach (Ed.), Information Processing in Motor Control and Learning, Academic Press, New York, 1978, pp. 117–152.

[47] D.T. Stuss, D.F. Benson, The Frontal Lobes, Raven Press, New York, 1986.

[48] J.J. Summers, Motor programs, in: D.H. Holding (Ed.), Human Skills, Wiley, Chichester, 1989, pp. 48–69.

[49] J. Talairach, P. Tournoux, Co-planar stereotaxic atlas of the human brain, Thieme, Stuttgart, 1988.

[50] J. Tanji, K. Shima, Role for supplementary motor are cells in planning several movements ahead, Nature 371 (1994) 413–416.

[51] J. Tanji, K. Shima, Supplementary motor cortex in organization of movement, Eur. Neurol. 36 (1996) 13–19.

[52] J.-L. Truelle, D. Le Gall, P.-A. Joseph, G. Aubin, C. Derouesné, M.D. Lezak, Movement disturbances following frontal lobe lesions: qualitative analysis of gesture and motor programming, Neuropsychiatry Neuropsychol. Behav. Neurol. 8 (1995) 14–19.

[53] S. Van Oostende, P. Van Hecke, S. Sunaert, B. Nuttin, G. Marchal, FMRI studies of the supplementary motor area and the premotor cortex, Neuroimage 6 (1997) 181–190.

[54] W.B. Verwey, Buffer loading and chunking in sequential keypressing, J. Exp. Psychol.: Hum. Percept. Perform. 22 (1996) 544–562.

[55] K.J. Worsley, A.C. Evans, S. Marrett, P. Neelin, A three-dimensional statistical analysis for rCBF activation studies in human brain, J. Cereb. Blood Flow Metab. 12 (1992) 900–918.