

## Single-neuron activity in the human supplementary motor area underlying preparation for action

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**Object.** The supplementary motor area (SMA) is considered critical in the planning, initiation, and execution of motor acts. Despite decades of research, including electrical stimulation mapping in patients undergoing neurosurgery, the contribution of this region to the generation of motor behavior has remained enigmatic. This is a study of single-neuron responses at various stages of a motor task during depth electrode recording in the SMA, pre-SMA, and medial temporal lobe of humans, with the goal of elucidating the disparate roles of neurons in these regions during movements.

**Methods.** The patients were undergoing evaluation for epilepsy surgery requiring implantation of intracranial depth electrodes. Single-unit recordings were made during both the execution and mental imagery of finger apposition sequences.

Only medial frontal neurons responded selectively to specific features of the motor plan, such as which hand performed the motor activity or the complexity of the sequence. Neuron activity progressively increased before the patient was given a “go” cue for the execution of movements; this activity peaked earlier in the pre-SMA than in the SMA proper. We observed similar patterns of activation during motor imagery and actual movement, but only neurons in the SMA differentiated between imagined and real movements.

**Conclusions.** These results provide support at the single-neuron level for the role of the medial frontal cortex in the temporal organization and planning of movements in humans.

**KEY WORDS** • supplementary motor area • presupplementary motor area • motor planning • motor imagery • human single unit • medial temporal lobe

**T**UMORS, vascular malformations, and other lesions such as cortical dysplasias sometimes involve the mesial surface of the frontal lobe in the region known as the SMA. Neurosurgeons have been among the earlier researchers interested in this region in the human brain. Penfield and Welch<sup>43</sup> defined the human SMA more than 50 years ago, but its contribution to the generation of complex motor behavior has remained enigmatic. Several lines of evidence suggest that the SMA plays a role in the temporal organization of movements, particularly the ability to generate a sequence of movements in response to a stimulus in the environment. Patients with bilateral lesions of the SMA suffer from akinesia and lose the ability “to get ready to move at a particular time.”<sup>30</sup> Electrical stimulation of the human SMA elicits the “urge” to move or the “anticipation” that a movement is about to occur.<sup>11,12,32</sup> Repetitive TMS of the human SMA interferes with the execution of future, rather than ongoing elements in a complex motor sequence.<sup>16</sup>

Cerebral blood flow studies of the human SMA show changes in the SMA during motor planning regardless of whether the movement is actually executed.<sup>49</sup> Both PET and

fMR imaging studies substantiate the role of the SMA in the preparation of movements.<sup>1,26,44</sup> Cortical potential studies have demonstrated that the “Bereitschafts potential” at scalp sites above the SMA is as long as 2 seconds before voluntary movements.<sup>8,9,19,21</sup> This slow wave of “readiness potential” occurs earlier in the SMA than in any other cortical area.<sup>8</sup> This type of potential has also been recorded when a person plans a movement that is never executed.<sup>31</sup>

In nonhuman primates the SMA is known to be active during the preparatory period before self-initiated motor acts.<sup>2,3,5,29,35,48,57,58,62</sup> Primate studies have shown that SMA neurons are active during the delay period before the start of the movement.<sup>53,54</sup> Several studies have demonstrated that a majority of neurons in the SMA are active as early as 1.6 seconds before movement in a new sequence, thus supporting the role of the SMA in the preparation of sequential motor tasks.<sup>3,33,39,57,58</sup>

Based on anatomical and physiological criteria, the SMA has been subdivided into a rostral SMA (the presupplementary area or pre-SMA) and a caudal SMA (the SMA proper).<sup>33,34,45,58</sup> Several authors have suggested differences in the connectivity of the two areas. Whereas most of the input to the SMA proper is from the primary motor cortex, the pre-SMA receives major input from the prefrontal cortex.<sup>33,34,39,45,58,62</sup> Based on the findings of these and other studies, it has been proposed that the pre-SMA participates in the selec-

*Abbreviations used in this paper:* ANOVA = analysis of variance; fMR = functional magnetic resonance; PET = positron emission tomography; SMA = supplementary motor area; TMS = transcranial magnetic stimulation.

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tion and updating of movements rather than in the initiation of the movement itself.<sup>57,58</sup>

Although electrical stimulation studies of the human medial frontal cortex have not shown the clear distinction between the SMA and pre-SMA that has been seen in nonhuman primates, recent fMR imaging and PET studies have been suggestive that such a division might also exist in the human brain. Evidence from both fMR imaging and PET support the idea originating from primate studies that the pre-SMA region is important for the selection and preparation of movement, whereas the SMA proper plays a motor executive role.<sup>1,26,44</sup> The somatotopic organization of the human SMA in the medial aspect of the frontal lobe is well established,<sup>12,32</sup> with the representation of the head and face anteriorly, that of the hand behind the latter, and the leg represented posteriorly, just in front of the leg representation in primary motor cortex. The location of the pre-SMA is thought to be anterior to the face representation in the SMA in humans. The border separating the SMA proper and the more anterior pre-SMA may, therefore, be the ventral anterior commissure plane.<sup>66</sup> It has been suggested that anterior medial frontal sites where electrical stimulation commonly elicits arrest of speech and other motor activity are a part of the human pre-SMA.<sup>11</sup>

Mental chronometry studies have indicated that mental motor imagery uses the same cortical structures and activates the same processes as movement preparation.<sup>15,52</sup> The time taken to perform mentally a movement is similar to the time necessary to execute the movement,<sup>25</sup> and these movements are constrained by a speed-accuracy tradeoff (the Fitt law) that applies to movement execution.<sup>65</sup> Furthermore, fMR imaging and PET studies have demonstrated that the same regions (for example, the pre-SMA, SMA, premotor, parietal, and basal ganglia regions) that are active during motor performance are also active during motor imagery.<sup>15,17,60</sup> From this model of motor imagery we can infer that the same areas would be active during the execution and mental motor imagery of a motor program, except at the final output stage, at which no activation is seen during motor imagery.<sup>17,23,25</sup>

A role for the medial temporal lobe, specifically the hippocampus, in sensory integration and planning for movements has been suggested in some studies.<sup>41,42</sup> Nevertheless, few studies on the role of the medial temporal lobe in the programming of movements and motor imagery during motor preparation have been performed in humans. Most studies have focused on the role of the medial temporal lobe in memory tasks, especially those concerned with integrating or combining information from various sources or events.<sup>10,37,38</sup>

We used a rare opportunity to conduct single-neuron recording in the SMA in humans during the selection, preparation, and execution of sequences of movements as well as during motor imagery. Recordings were conducted in patients undergoing monitoring of intracranial electroencephalographic activity, which was performed using depth electrodes for potential resective neurosurgery. Single-unit data in humans are critical for integrating findings from extracellular recordings in trained animals and hemodynamic changes obtained by neuroimaging studies in humans. Furthermore, certain aspects of motor planning, such as motor imagery, can only be studied in humans. Taken together these data may offer a better understanding of the

function of the SMA in the normal brain as well as in the presence of parenchymal lesions.

### Clinical Material and Methods

#### Patient Population

Thirteen patients with pharmacologically intractable epilepsy comprised the study group. The patients ranged in age from 16 to 49 years. Nine of the patients were men and 12 were right-handed. Extensive noninvasive monitoring did not yield concordant data corresponding to a single resectable focus and thus the patients were stereotactically implanted with up to 12 long-term depth electrodes for 1 to 2 weeks to determine the seizure focus for possible resection. The electrode locations were based exclusively on clinical criteria. All studies conformed to the guidelines of the Medical Institutional Review Board at the University of California at Los Angeles. The implantation procedure and detailed characteristics of the electrodes have been described previously.<sup>4,13,14,27</sup> The electrodes were all placed in lateral trajectories, orthogonal to the stereotactic frame. Eight microwires (each 40  $\mu\text{m}$  in diameter) were inserted through the lumens of the electrodes. The locations of the electrodes were verified by structural MR imaging, which was performed before removal of the electrodes. The individual microwires extended approximately 4 mm from the tip of the electrode, lying in a cone with an opening angle smaller than 45°.

We report on the activity of neurons for all probes located in the SMA proper, in the pre-SMA, and in the medial temporal lobe (in the amygdala, entorhinal cortex, and hippocampus). The regional distribution of neurons recorded from each patient was as follows: in the pre-SMA a total of 35 cells were recorded in Cases 1 (seven neurons), 3 (six neurons), 4 (six neurons), 5 (one neuron), 6 (10 neurons), and 7 (five neurons). In the SMA a total of 26 cells were recorded in Cases 1 (two neurons), 2 (two neurons), 4 (five neurons), 6 (seven neurons), 9 (three neurons), 10 (3 neurons), 11 (two neurons), and 13 (two neurons). In the medial temporal lobe a total of 39 cells were recorded in Cases 1 (four neurons), 5 (two neurons), 6 (three neurons), 7 (five neurons), 8 (three neurons), 9 (eight neurons), 10 (two neurons), 11 (two neurons), 12 (three neurons), and 13 (six neurons). We realize that generalizations about normal neuronal function based on recordings made in patients with epilepsy constitute a potential limitation of this study; however, 82% of the recorded neurons lay outside the clinically determined epileptogenic zone, and we did not observe differences in waveforms, firing rates, interspike interval distributions, or response properties in neurons near or distant from the seizure focus.

#### Behavioral Paradigms

The behavioral paradigms consisted of either an executed or imagined cued fingers-to-thumb apposition task (Fig. 1). Each finger was numbered from the index finger (1) to the little finger (4), and the patient had to touch the thumb of the appropriate hand (left or right) to the corresponding finger in the proper sequence, after it had been presented on a computer monitor. In the "simple" task, numbers were repeated (111, 222, 333). In the "complex" task, numbers were given in random order without repetition (231, 312,

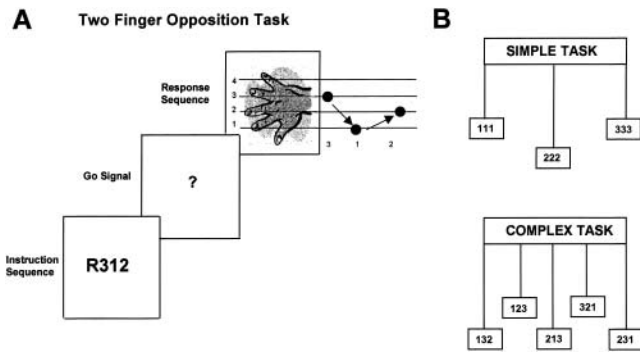


FIG. 1. Diagram demonstrating the finger-to-thumb apposition task. A: Each trial began with the appearance of an instruction cue for 5 seconds. The appearance of the question mark symbol (?) 5 seconds after onset of the instruction cue was the go signal for execution of the movement. The arrows indicate the required sequence of movements. B: Sample instruction cues for simple and complex tasks.

132, 213). Left (L) or right (R) notations preceding the numbered sequence informed the patient as to which hand should be used in performing the task. In both tasks a trial began with the onset of the instruction cue (for example, L213, R123). The patient was required to fixate on the instruction cue for 5 seconds. A question mark (?) appearing 5 seconds after onset of the instruction cue was the “go” signal for execution of the movement. The patient was instructed either to execute the required sequence of movements or to imagine performing the sequence immediately after onset of the go signal (Fig. 1A).

*Recordings From Microwires*

Data from each of the recording microwires were amplified and high-pass filtered (with a corner frequency of 300 Hz), converted from analog to digital, and stored for offline spike sorting by using data acquisition software (Experiment Workbench; Datawave, Denver, CO).<sup>13,14</sup> Two milliseconds of electrophysiological activity surrounding each triggered action potential was digitized at 20 kHz, and multiple units were separated based on the action potential, amplitude, duration, slope, and other parameters of waveform morphology.<sup>36</sup> Note that because the microelectrodes were implanted in fixed positions, we could not further select neurons by moving the electrodes, as is the case for experiments in primates.

*Statistical Analysis*

Spike counts were obtained for 200-msec bins and collapsed across 1-second epochs: the second before the instruction onset ( $T_0$ ), the 1st second during which the instruction cue was presented ( $T_1$ ), the following 4 seconds prior to the go signal ( $T_2$ – $T_5$ , the delay period), and the period following the go signal ( $T_6$ – $T_8$ ). We evaluated the activity of each neuron by using pairwise t-test comparisons of mean firing rates during the relevant time intervals and baseline rates. Significant changes in neuronal activity were increases or decreases in mean firing rates compared with baseline values ( $p < 0.05$ ). A separate repeated-measures ANOVA was performed for each unit of firing rates during the instruction period ( $T_1$ ), during the second before the onset

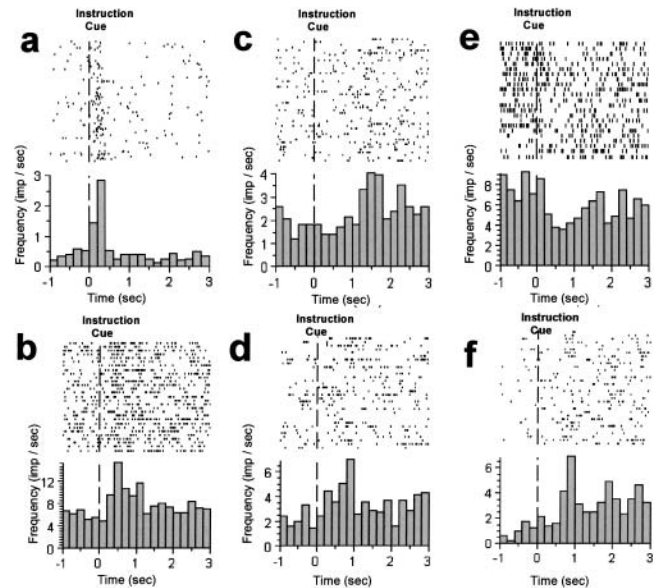


FIG. 2. Neuronal responses to the instruction cue. Rasters and histograms (0.2-sec bins) of pre-SMA, SMA proper, and hippocampal neurons responding to the cue. The vertical dashed line indicates onset of the instruction cue. Significant increases in the neuronal discharge rates ( $p < 0.05$ ) of neurons in both the pre-SMA (a) and SMA proper (b) following presentation of the instruction cue. Example of a neuron in the pre-SMA (e) that displayed a decreased firing rate below baseline following presentation of the instruction cue. Neurons in the pre-SMA (c), SMA proper (d), and hippocampus (f) exhibited a gradual increase in the firing rate after the onset of the instruction cue, reaching a maximum firing rate at 0.8 to 2 seconds following onset of the instruction cue.

of the go signal ( $T_0$ ), and during 1 second of the motor response phase ( $T_6$ ). The repeated measures for each time period were corrected for baseline values. Factors in the ANOVA included task difficulty (simple compared with complex) and hand used (ipsilateral compared with contralateral to the recorded unit). We considered a unit to have a differential response to a factor when the factor or its interaction with time was significant ( $p < 0.05$ ).

Although neurons were considered to show selective responses if ANOVA results were significant at a probability level lower than 0.05, many responses were significant at a probability level lower than 0.01. Given the number of cells and the number of ANOVA tests, a few such significant results might be expected by chance among the population of neurons from which the recordings were made. To address this concern we followed a procedure used by Rolls and colleagues<sup>50,51</sup> in which one computes the number of cells with significant results at each level (that is,  $p = 0.05$ – $0.01$ ;  $p = 0.01$ – $0.005$ ;  $p = 0.005$ – $0.001$ ; and  $p < 0.001$ ) found in the ANOVA and compares this number, by using a goodness-of-fit chi-square test, with the number that would be expected by chance. Rejection of the “fit” implies that the number of cells with significant results is not merely due to chance. In computing the expected number of significant units by chance alone, we took into account the fact that a factor was considered significant if its main effect or interaction with time were significant. Thus, the expected number of chance units were increased accordingly.

**Results**

We recorded the activity of 100 neurons in 13 patients during the performance of the finger-to-thumb apposition task (61 neurons in the medial frontal cortex, and 39 neurons in the medial temporal cortex). Of these 100 neurons, 36 were also recorded during motor imagery (14 neurons in the medial frontal cortex and 22 in the medial temporal cortex). The distribution of neurons across patients for the various regions is described in *Clinical Material and Methods*.

*Neuron Responses to the Instruction Cue*

Three types of instruction responses were observed in the medial frontal cortex. The first was characterized by an increase in discharge rate, which occurred approximately 200 msec after onset of the instruction cue (Fig. 2a) and sometimes persisted throughout the 1st second of presentation (Fig. 2b). The second type of response to the visual instruction cue was characterized by a later increase in the neuron firing rate, which peaked approximately 1000 msec after onset of the instruction cue and, sometimes, even as late as 1600 msec (Fig. 2c and d). The third response type was characterized by a sharp decrease in the firing rate, which occurred between 200 and 400 msec after onset of the instruction cue (Fig. 2e).

The responses to the instruction cues observed in the temporal lobe were similar to the first two types of responses observed in the medial frontal lobe. The first consisted of an increase in firing immediately after the presentation of the instruction cue, whereas the second more common type was characterized by a burst of activity at the end of the 1st second after cue onset (Fig. 2f).

Neuron discharge rates were examined during the second following onset of the instruction cue ( $T_1$ ). The neuron response during  $T_1$  was compared with the neuron response during baseline ( $T_0$ ). A neuron was considered to be responsive if there was a significant difference in the neuron firing rate during the instruction period when compared with the baseline value for any one of the four conditions: left side, right side, easy task, or difficult task. A Student paired t-test revealed that 25 (41%) of the medial frontal units and nine (23.1%) of the medial temporal units displayed an altered neuronal firing rate in response to the cue presentation (Table 1).

The number of medial frontal neurons that responded to the instruction cue was not significantly greater than the number in the medial temporal cortex ( $\chi^2 = 3.39$ ,  $df = 1$ ,  $p > 0.05$ ). A goodness-of-fit chi-square test was applied to

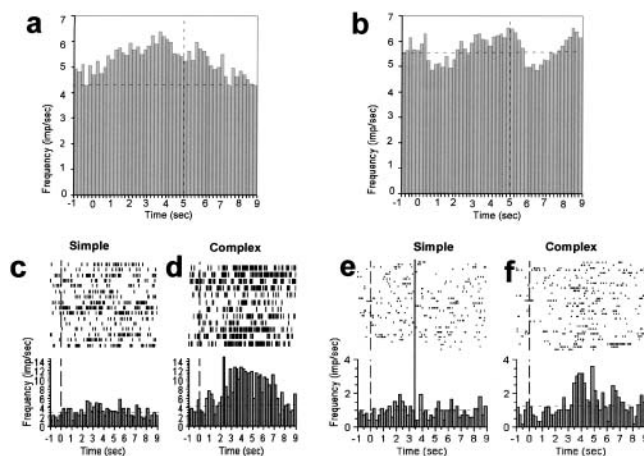


FIG. 3. Neuronal activity during the delay period. Compound histograms of 12 neurons in the pre-SMA (a) and nine neurons in the SMA proper (b) that displayed a progressive increase in neuronal activity during the delay period starting as early as 1 second after onset of the instruction cue. Vertical dashed lines denote onset of the go signal instructing the patient to perform the motor task. Rasters and histograms for a pre-SMA neuron (c and d) and an SMA-proper neuron (e and f) whose neuronal discharge rates during the delay period was significantly greater for the complex task than during the performance of the simple task.

these data to examine the hypothesis that the number of significantly responding neurons might have been due to chance. This hypothesis was rejected for the medial frontal cortex ( $\chi^2 = 166.3$ ,  $p < 0.0001$ ) and for the medial temporal cortex ( $\chi^2 = 26.8$ ,  $p < 0.0001$ ).

*Neuron Activity During the Delay Period*

During the delay period (the 4 seconds preceding the go signal) the majority of neurons in the medial frontal cortex (21 [80.8%] of 26 neurons in the SMA proper and 29 [82.9%] of 35 neurons in the pre-SMA) displayed an increased neuronal firing rate compared with the baseline value (Table 1). The difference in the number of pre-SMA and SMA neurons that responded during the delay period was not significant ( $\chi^2 = 0.04$ ,  $p > 0.05$ ). The responses of neurons in both the SMA proper and the pre-SMA during the delay period were characterized by a gradual increase in the firing rate. Figure 3 shows the compound histograms of nine SMA and 12 pre-SMA neurons for which there was a characteristic increase in neuron firing frequency for at least 2 seconds of the 4-second delay period. The mean firing

TABLE 1  
*Neurons responding during various phases of the motor task\**

Phase of Motor Task	No. of Neurons (%)			
	Pre-SMA (35 neurons)	SMA Proper (26 neurons)	Medial Frontal Lobe (61 neurons)	Medial Temporal Lobe (39 neurons)
cue period	15 (42.9)	10 (38.5)	25 (41.0)	9 (23.1)
delay period	29 (82.9)	21 (80.8)	50 (82.0)	19 (48.7)
response period	26 (74.3)	20 (76.9)	46 (75.4)	16 (41.0)

\* The medial frontal lobe includes both the pre-SMA and the SMA proper. The medial temporal lobe includes the amygdala, entorhinal cortex, and hippocampus. In all instances the number of significantly responding neurons in each region was greater than what would be expected due to chance according to a goodness-of-fit chi-square test.

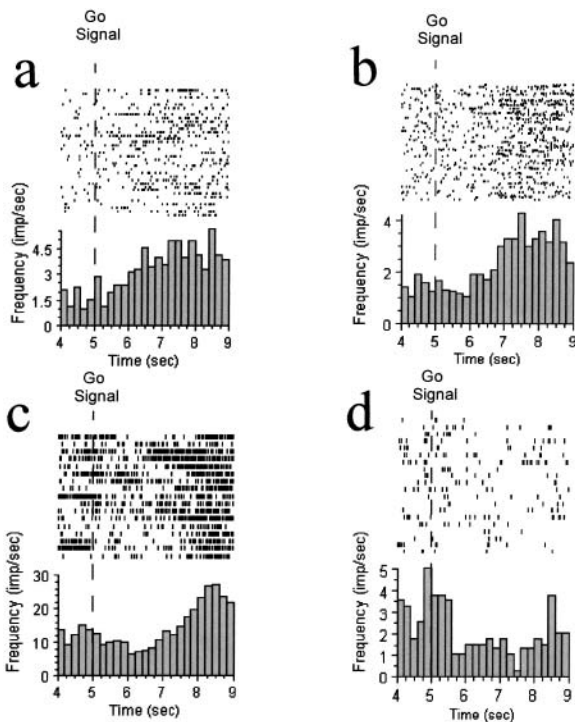


FIG. 4. Neuronal activity during the motor response. Rasters and histograms for a pre-SMA neuron (a) and for SMA-proper neurons (b and c) displaying increases in the firing rate during the motor response phase and a hippocampal neuron (d) whose firing rate peaked at the onset of the go signal, but was inhibited during the motor response phase. Vertical dashed lines denote onset of the “go” signal for execution of the motor task.

rate during the delay period was  $5.72 \pm 0.5$  impulses/second for SMA neurons and  $5.3 \pm 0.55$  impulses/second for pre-SMA neurons. Delay period activity was sometimes present only for complex tasks, but not for simple tasks (Fig. 3c–f).

When the peak latency of the rise in firing rates of individual neurons was compared between the two regions, pre-SMA neurons peaked earlier than SMA neurons. The average peak response of pre-SMA neurons occurred at  $4170 \pm 350$  msec, that is, 830 msec before the go signal, whereas the peak response of SMA neurons occurred at  $5200 \pm 330$  msec, that is, 200 msec after the go signal. Both parametric (unpaired samples t-test,  $t = -6.845$ ,  $df = 19$ ,  $p < 0.0001$ ) and nonparametric tests (Mann–Whitney U-test;  $Z = 3.695$ ,  $p < 0.0002$ ) showed that the peak response of pre-SMA neurons was significantly earlier than the peak response of SMA neurons. In fact all 12 pre-SMA neurons peaked before the go signal was given, whereas eight of nine SMA neurons peaked after the go signal.

During the delay period 19 (48.7%) of 39 medial temporal lobe neurons displayed significantly altered neuronal firing rates compared with baseline values (Table 1). There was a significantly greater number of medial frontal neurons (50 [82%] of 61 neurons) responding during the delay period ( $\chi^2 = 12.3$ ,  $p < 0.01$ ). A goodness-of-fit chi-square test was applied to these data to examine the hypothesis that the number of significantly responding neurons might have been the result of chance. This hypothesis was rejected for

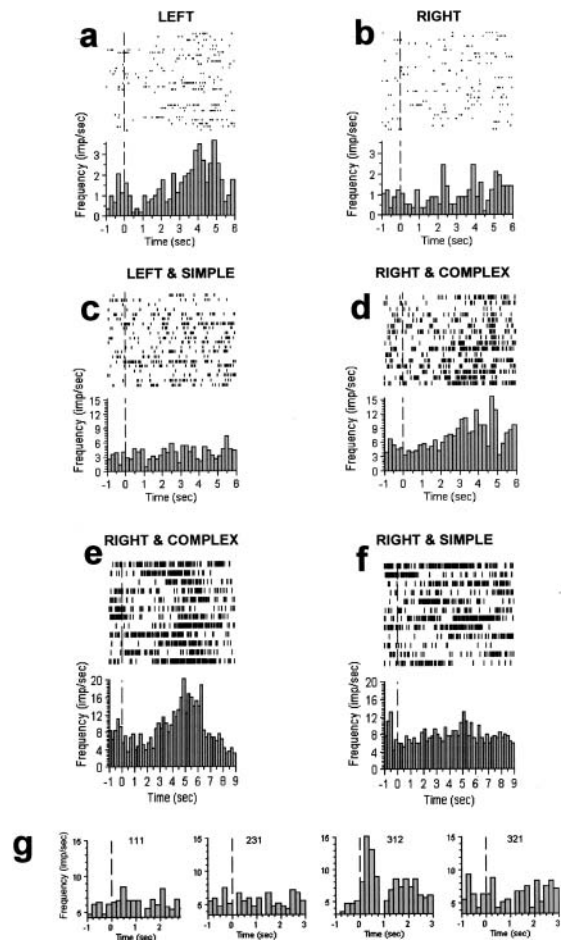


FIG. 5. Examples of selectivity to features of the task. a and b: Right SMA neuron whose firing rate during the delay was significantly greater when the task required the use of the left hand as opposed to the right hand ( $p < 0.01$ ). c and d: Neuron in the left SMA that displayed an increased firing rate during the delay period preceding the execution of complex motor sequences by the right hand. Note that there was no response during the delay period preceding the simple sequence performed by the left hand. e and f: Left medial amygdala neuron whose neuronal discharge rate during the delay period was significantly greater during the execution of a complex (e), as opposed to a simple (f) movement sequence when the right hand was used. g: Neuron in the pre-SMA exhibiting a sequence-selective response during the 1st second after presentation of the instruction cue. The three-digit number above each histogram denotes the specific motor sequence of finger apposition. The preferred sequence is 312. One-way ANOVA showed significant differences between the neuron’s responses to the various sequences ( $p < 0.025$ ). Vertical dashed lines denote onset of the instruction cue.

the medial frontal cortex ( $\chi^2 = 163$ ,  $p < 0.0001$ ) and the medial temporal cortex ( $\chi^2 = 23.6$ ,  $p < 0.0001$ ).

*Movement-Related Activity*

Typical neuron responses observed in the medial frontal cortex during motor activity were characterized by an increased firing frequency that occurred 1 to 3 seconds after the go signal (Fig. 4a–c). This response was sometimes preceded by a decrease in the firing rate during the 1st second after the go signal (Fig. 4c).

TABLE 2

*Neurons with selective responses to features of the motor task (complexity, hand laterality, or their conjunction)*

Task Features	No. of Neurons (%)			
	Pre-SMA (35 neurons)	SMA Proper (26 neurons)	Medial Frontal Lobe (61 neurons)	Medial Temporal Lobe (39 neurons)
simple vs complex	11 (31.4)*	8 (30.7)*	19 (31.1)*	3 (7.7)
left vs right	8 (22.9)*	7 (26.9)*	15 (24.6)*	2 (5.1)
simple vs complex & left vs right	8 (22.9)*	4 (15.4)	12 (19.7)*	1 (2.6)

\* The number of selective neurons in this region is greater than what would be expected due to chance according to a goodness-of-fit chi-square test.

In contrast to the 46 (75.4%) of 61 medial frontal neurons that exhibited an altered neuronal discharge rate during the motor response phase, only 16 (41%) of 39 medial temporal neurons responded during this phase ( $\chi^2 = 11.93$ ,  $p < 0.05$ ; Table 1). The response of medial temporal neurons was often characterized by a decreased firing rate, approximately 400 to 600 msec, following the go signal (Fig. 4d). The hypothesis that the number of significantly responding neurons might have been a result of a change was rejected for the medial frontal cortex ( $\chi^2 = 131$ ,  $p < 0.0001$ ), as well as for the medial temporal cortex ( $\chi^2 = 13.1$ ,  $p < 0.0002$ ).

#### Task Selectivity

To assess the effect of laterality (that is, the hand used to perform the task) as well as the complexity of the task on the firing rate, a repeated-measures ANOVA was performed during the instruction period ( $T_1$ ), during the second before onset of the go signal ( $T_5$ ), and during 1 second of the motor response phase ( $T_6$ ). Nineteen (31.1%) of 61 medial frontal neurons (11 [31.4%] of 35 pre-SMA neurons and eight [30.7%] of 26 SMA-proper neurons) as opposed to three (7.7%) of 39 medial temporal neurons differentiated between simple and complex tasks (Table 2). This difference between the two areas was significant ( $\chi^2 = 7.63$ ,  $p < 0.05$ ). To test the hypothesis that these percentages are due to chance, we performed a goodness-of-fit test and rejected the hypothesis for medial frontal neurons ( $\chi^2 = 6.5$ ,  $p < 0.01$ ), but not for medial temporal neurons ( $\chi^2 = 3$ ,  $p < 0.08$ ).

Fifteen of 61 medial frontal neurons (eight (22.9%) of 35 pre-SMA neurons and seven (26.9%) of 26 SMA-proper neurons) and two (5.1%) of 39 medial temporal neurons displayed a significant difference between the neuron response rates for ipsilateral and contralateral movements (Table 2). The difference in the number of neurons in the medial frontal and medial temporal cortices demonstrating a laterality effect was significant ( $\chi^2 = 5.72$ ,  $p < 0.05$ ). The number of neurons that displayed a laterality effect was higher than could be expected by chance for the medial frontal cortex ( $\chi^2 = 17.1$ ,  $p < 0.0004$ ), but not for the medial temporal cortex ( $\chi^2 = 37.83$ ,  $p < 0.99$ ). An example of a right SMA neuron that exhibited a preferential response to the contralateral (left) hand during the delay period is provided in Fig. 5a and b. Twelve (19.7%) of 61 medial frontal neurons and only one (2.6%) of 39 medial temporal neurons responded during particular combinations of laterality and complexity (Table 2). The difference between the two areas was significant ( $\chi^2 = 6.46$ ,  $p < 0.05$ ). An example of a medial frontal (left SMA) neuron that exhibited an increased firing rate only in response to particular com-

binations of laterality and complexity is shown in Fig. 5c and d. This neuron responded selectively during the delay period preceding execution of complex but not simple sequences, but only when performed with the contralateral (right) hand. The only medial temporal neuron, one in the amygdala, responding to the combination of laterality and complexity is shown in Fig. 5e and f. In addition, there were medial frontal neurons that responded selectively to particular sequences of finger apposition. An example of a sequence-selective neuron in the pre-SMA is depicted in Fig. 5g.

#### Motor Imagery

To compare neuronal activity during motor imagery and during actual motor performance, we performed ANOVA at various phases of the task. During the instruction period ( $T_1$ ), three of 14 neurons in the medial frontal cortex and one of 22 in the medial temporal lobe differentiated between real and imagined conditions. A goodness-of-fit test was performed to see if any of these responses could be due to chance. This hypothesis was rejected for medial frontal neurons ( $\chi^2 = 8$ ,  $p < 0.004$ ) but not for medial temporal neurons ( $p > 0.92$ ).

During the last second of the delay period ( $T_5$ ), four of 14 medial frontal neurons and two of 22 medial temporal neurons differentiated between real and imagined conditions. The hypothesis that this could be due to chance was also rejected for medial frontal neurons ( $\chi^2 = 16.4$ ,  $p < 0.0005$ ), but not for medial temporal neurons ( $\chi^2 = 0.8$ ,  $p > 0.37$ ).

During the 1st second of the motor response period ( $T_6$ ), four of 14 medial frontal neurons and three of 22 medial temporal neurons differentiated between imagined and executed movements. The hypothesis that these findings could be due to chance was rejected for the medial frontal lobe ( $\chi^2 = 16.4$ ,  $p < 0.0005$ ), but not for the medial temporal lobe ( $\chi^2 = 3.5$ ,  $p > 0.06$ ).

Thus, the main differences between neuron responses during motor imagery and actual movements were seen in the SMA and not in the medial temporal lobe. Some SMA neurons displayed increased firing rates after presentation of an instruction signaling that a real, rather than an imagined, movement would have to be executed on that trial (Fig. 6a and b). Interestingly, some neurons displayed stronger responses during imagined movement sequences than during actual execution of these sequences (Fig. 6c and d). During the motor response period, some SMA neurons displayed significantly increased neuron activity during real movements performed using a specific hand compared with imagined movements with the same hand (Fig. 6e and f). Nevertheless, there were also neurons that responded in a

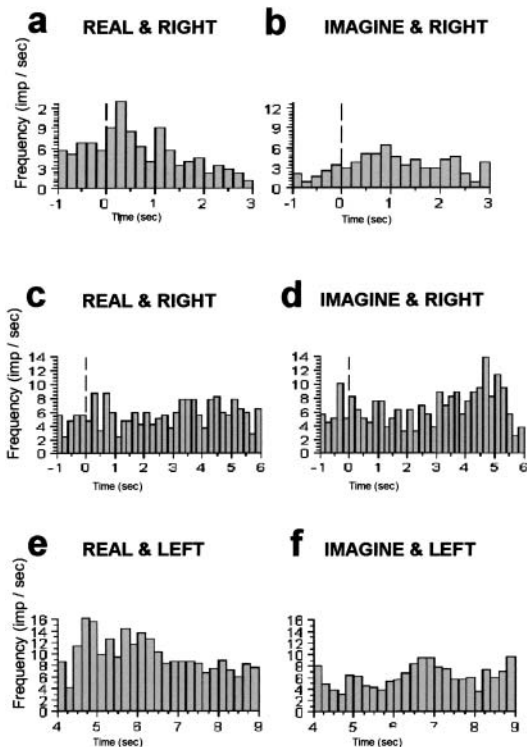


FIG. 6. Responses of SMA neurons during imagined and real motor sequences. Histograms (0.2-sec bins) are shown. The vertical dashed lines indicate onset of the instruction cue. a and b: An SMA neuron active during the real condition, but not during the imagined condition ( $p < 0.01$ ). c and d: Neuron in the SMA whose firing rates were greater during trials when the patient had to imagine performing the task with his right hand. e and f: An SMA neuron whose firing rate during the motor response period was greater when the patient had to perform a “real” movement with his left hand.

similar manner during imagined and real movement sequences (Fig. 7). This occurred in both the simple tasks (Fig. 7a and b) and complex tasks (Fig. 7c and d). There were neurons that responded selectively during the left- or right-handed task or during a particular sequence that did so in the same selective manner during motor imagery (Fig. 7e–h).

## Discussion

In this study we have shown changes in the activity of both medial frontal and medial temporal neurons during the instruction, planning, and execution phases of a motor task. Nevertheless, the percentage of neurons demonstrating these responses was significantly greater in medial frontal areas (the SMA and pre-SMA regions) than in the mesial temporal areas (amygdala, entorhinal cortex, and hippocampus). Furthermore, only medial frontal neurons exhibited selective responses to particular features of the motor plan, that is, the laterality of the performing fingers (ipsilateral or contralateral to the site of the neuron), the complexity of the movement sequence, or combinations of these two variables. Selective neuron responses to visually prescribed complex or simple sequences (Fig. 5c and d) as well as selective responses to individual sequences (Fig. 5g) indicate that the activity of medial frontal neurons reflects in-

formation about the stimuli; this information is then used for planning the motor response.<sup>18,59</sup> In addition, only medial frontal neurons differentiated between tasks of real and imagined motor sequences. It should be pointed out, however, that only a small number of neurons were tested with motor imagery and the results reported here should be regarded as preliminary.

These findings indicate that neurons in the SMA and pre-SMA encode motor plans, and the data provide support at the single-neuron level for the role of the human medial frontal cortex in the planning and temporal organization of movements. This study therefore complements observations in patients with medial frontal lesions,<sup>30</sup> studies of this region in which electrical stimulation<sup>12,32</sup> and TMS have been used,<sup>16</sup> and mapping of these areas using neuroimaging techniques.<sup>1,26,44,49</sup> In addition, the findings in this study extend observations in nonhuman primates regarding the activity of single neurons during the preparation and initiation of motor acts.<sup>1,26,44</sup>

Of particular interest is the increase in neuronal discharges seen in medial frontal neurons in humans in preparation for action. This increase was not merely a correlate of waiting but was dependent on the content of the motor task to be performed. It was often more pronounced for complex sequences compared with the relatively simple repetitive finger movements. This delay activity cannot be solely attributed to the “on-line” maintenance of the memory trace of the instructions, because the information prescribing the motor sequence was visually present for the entire delay period. It could, however, signal the preparation or updating of the motor plan that occurs in response to the presentation of the instruction cue. The role of the SMA in preparation for movements is supported by findings of animal studies.<sup>57,58</sup> Reports by Brinkman and Porter<sup>3</sup> and Tanji and Kurata<sup>63</sup> indicate that the SMA may be involved in the preprogramming of movements such that the appropriate preparatory state is developed in response to an advance instruction. Indeed, single-neuron recordings in monkeys have shown increased neuronal activity in the SMA during the delay period, which continued until the signal that triggered the movement occurred.<sup>63</sup> This activity was not temporally related to the onset of the movement, but rather to the events involved in preparation for future initiation of a movement. Therefore, the progressive increase in activity that we observed during the delay period in the SMA could represent the underlying preparatory process required to perform successfully an externally triggered but internally generated sequence of movements. This activity may occur during the early motor processing stage when the patient feels the “urge” to perform the instructed movement sequence.<sup>11,12</sup>

The gradual increase in SMA single-neuron activity is temporally similar to that of cortical potentials that are recorded in humans before movement. These potentials include the “Bereitschafts potential,” or readiness potential, which is recorded before internally generated voluntary movements by using scalp electrodes,<sup>7,9,46,47</sup> and the slow negative brain potentials that occur between two associated stimuli, that is, the contingent negative variation described by Walter and associates.<sup>64</sup> Most authors attribute the readiness potential to activation of the SMA.<sup>46</sup> According to Deecke, et al.,<sup>8</sup> this slow wave occurs earlier in the SMA than in any other cortical area (including the primary motor

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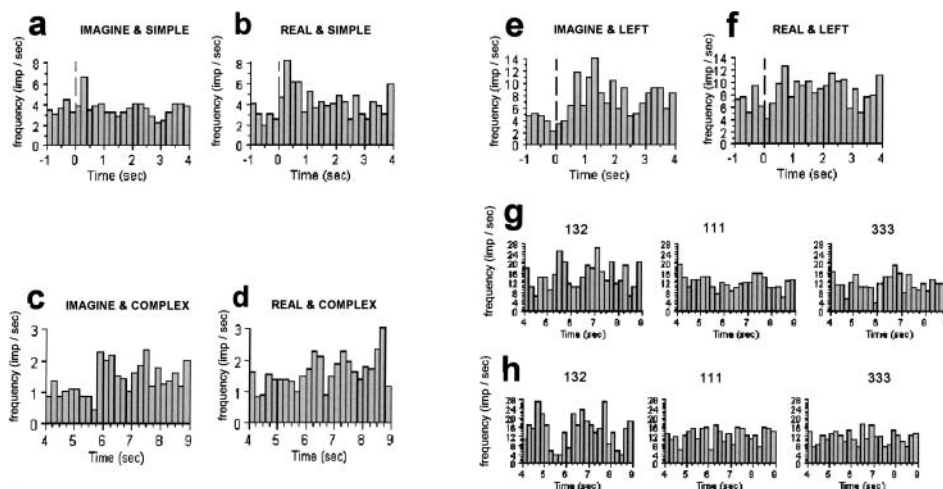


FIG. 7. Responses of SMA neurons during imagined and real motor sequences. a and b: Neuron in the SMA, which is active during the instruction cue phase of the imagined and real movement tasks involving simple sequences. c and d: An SMA neuron displaying increased activity during the response phase of both imagined and executed motor sequences. For both real and imagined conditions, neuron activity was greater during complex than simple sequences. e and f: Neuron in the SMA is active during imagined and executed movements of the left (but not the right) hand. g and h: Neuron in the SMA with similar sequence-specific responses during imagined (g) and real (h) movement conditions.

cortex) and, similar to the delay activity in our study, varies with the complexity of the task.<sup>28</sup> This activity over the SMA is also present when individuals plan to move but do not subsequently perform a movement.<sup>31</sup> Such evidence suggests that the SMA may contribute to the intention to act by conveying readiness to act to downstream motor regions.<sup>3</sup> This view is also supported by repetitive TMS studies that demonstrate that stimulation during the delay period of the human SMA interferes with the execution of future motor sequences.<sup>16</sup> It is also consistent with cortical potential studies<sup>22</sup> and fMR imaging studies<sup>44</sup> in which researchers have found an increase in activity in the SMA when switching motor tasks or while performing working memory delay tasks, supporting the contribution of the SMA to the state of preparedness for selection of a motor response.

Our results support the notion of distinct specialized regions within the human SMA, that is, the SMA proper and the pre-SMA. In our study pre-SMA neurons peaked before the instruction cue, at an average of 4.1 seconds into the task, whereas SMA neurons peaked after the trigger, at an average of 5.2 seconds. There appears to be sequential activity that may involve the earlier selection or updating of the motor plan by the pre-SMA and later processing of information by the SMA proper, for the initiation of the movement. Our findings are consistent with reports of single-neuron studies in nonhuman primates that demonstrate similar changes in neuron activity in the SMA proper and the pre-SMA during the delay period before movements, but at the same time suggest differences between the two regions.<sup>35,39,57-59</sup> By studying the response of pre-SMA neurons during the performance of blocked trials, Shima, et al.,<sup>57</sup> found a group of pre-SMA neurons that were active during the delay period of the first trial of a new motor sequence. The early increase in activity that we observed in the human pre-SMA may be similar to what Shima, et al., found in their primate studies, because in the present study trials were completely randomized, and thus each was a new sequence.

An important feature of this study was the direct comparison of single-neuron activity in the SMA and pre-SMA with that in medial temporal lobe neurons during the various phases of the task. Although neurons in the medial temporal lobe displayed altered firing rates during the instruction, delay, and execution phases of the motor task, the activity of these neurons was not selective to the features of the task, namely, the complexity of the prescribed motor sequence or the laterality of the performing hand. These findings suggest that they do not play a significant role in the encoding of the motor plan. To our knowledge, there are only a few studies in which the role of the hippocampus and neighboring structures in the planning and performance of motor acts have been addressed. In the hippocampus of mammals, a sinusoidal-like rhythm (theta rhythm) is thought to be involved in coding for certain aspects of voluntary motor behavior—increases in theta rhythm reflect either increases in the velocity<sup>42</sup> or amplitude<sup>41</sup> of movements. This theta rhythm is noticeably absent in automatic behavior.<sup>42</sup> Lesions of the hippocampus or transections of the fimbria-fornix from the hippocampus abolish the theta rhythm and severely impair motor performance. The correlation between the theta rhythm and motor performance has led to the hypothesis that the hippocampus plays some role in the execution of movements.

In this study we were able to record the activity of SMA neurons during imagined motor sequences and to compare it directly with activity of medial temporal lobe neurons during the same task. Although the number of recorded neurons was small, this study provided information on movement-related mental activity that cannot be accessed in animals. Our results suggest that SMA neurons, rather than medial temporal lobe neurons, discriminate between imagined and real movements. Contrary to what might be expected, however, activity during motor imagery was not always weaker compared with actual movement; some neurons responded more vigorously during imagery of a movement sequence than during actual performance of the

sequence. Nevertheless, there were also neurons that responded in a similar manner during the motor imagery task and the actual movement task. An example is a neuron that responded to a particular sequence of finger apposition during actual movement and then responded selectively to this sequence during motor imagery. These findings provide confirmation by direct neuronal recording that there is a common neuronal substrate for motor imagery and the actual execution of movement, as suggested more indirectly by PET, fMR imaging, and event-related potential studies.<sup>6,24,52,56,61</sup>

### Conclusions

This is the first study in humans of the SMA at the single-neuron level during the preparation, execution, and imagery of motor acts. Neurons in the SMA responded selectively to specific features of the motor plan, such as which hand performed the motor activity or the complexity of the sequence. Medial temporal neurons did not show this specificity of their responses. In the SMA, neuronal activity progressively increased before a go cue for the the execution of movements, peaking earlier in the pre-SMA than in the SMA proper. We observed similar patterns of activation during motor imagery and actual movement, but only neurons in the SMA differentiated between imagined and real movements. These results provide support at the single-neuron level for the role of the medial frontal cortex in the temporal organization and planning of movements in humans.

The opportunity to record from this area in humans exists only in highly selected and rare clinical circumstances and, indeed, the number of neurons studied reflect these constraints. Nevertheless, these results complement and extend functional neuroimaging and scalp event-related potential studies in humans and neurophysiological studies in non-human primates, and provide a critical link between these fields of investigation. Neurosurgeons are in the unique position of treating patients with disorders involving the SMA. This is evidenced by early reports of Penfield and Welch,<sup>43</sup> as well as by several recent reports on preoperative mapping and functional consequences of surgical interventions in this area.<sup>20,40,55</sup> Opportunities like these should be diligently pursued to gain further insights into the functional organization of this region in humans.

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