Spatiotemporal brain dynamics during preparatory set shifting: MEG evidence

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Humans can flexibly alter a plan of action to adjust their behavior adaptively in changing environments. Functional neuroimaging has shown distinct patterns of activation across a frontoparietal network responsible for switching and updating such plans of action or 'task sets.' However, little is known about the temporal order of activations within prefrontal or across with posterior regions subserving set-shifting operations. Here, whole-head magnetoencephalography (MEG) was used to explore the spatiotemporal brain dynamics in a modified version of the Wisconsin card-sorting test (WCST). Our task was designed to examine preparation of set-shifting rather than set-acquisition operations time locked to context-informative cues. Three cortical regions showed a larger number of MEG activity sources in response to shift and relative to nonshift cues: (a) inferior frontal gyrus (IFG; BA 45, 47/12), (b) anterior cingulate cortex (ACC; BA 24, 32), and (c) supramarginal gyrus (SMG; BA 40). Importantly, the timing of MEG activation differed across these regions. The earliest shift-related MEG activations were detected at the IFG (100–300 ms postcue onset), followed by two further peaks at the ACC (200–300 and 400–500 ms) and the SMG (300–400 and 500–600 ms). Several other prefrontal and posterior cortical areas were similarly activated by both shift and nonshift preparatory cues. The resulting temporal pattern of interactions within prefrontal and across with posterior association cortices is coherent with current models of task switching and provides novel information about the temporal course of brain activations responsible for the executive control of attention.
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Introduction

In recent years, there has been a growing interest in the cerebral substrates of the executive control of human cognition. Task-switching paradigms have been widely employed to obtain reliable operational measures of executive control processes (Meiran et al., 2000; Rabbitt, 1997). In these paradigms, the subject needs to switch the task rules (or 'task set') according with prespecified and contextually relevant cues. Probably, the Wisconsin card-sorting test (WCST) has been one of the most widely used set-shifting paradigms in both clinical and research contexts (Milner, 1963). In the WCST, the subject is asked to match a given choice card with four key cards based on one of three stimulus dimensions: color, number, or shape of elements in the cards. At any one time, only one of those three rules determines correct task performance. After a variable number of card sorts according to a given dimension, a cue prompts the subject to discard the old sorting rule and to shift to a new one. The task rules are thus acquired and changed until all the cards have been sorted using all three possible rules. Healthy subjects have little difficulty with this task. In contrast, people with prefrontal damage can learn the first rule, but then they are unable to escape it: they make a great deal of errors because they lapse back to the earlier rule (Milner, 1963). The ability of monkeys with prefrontal cortical lesions to perform an adapted version of this task is also impaired (Miller, 2000; Nakahara et al., 2002).

Functional neuroimaging studies have used both WCST analogues and task-switching paradigms to examine the brain basis of the different component operations of this executive mechanism (Dove et al., 2000; Dreher and Berman, 2002; Dreher et al., 2002; Konishi et al., 1998; Luks et al., 2002; Monchi et al., 2001; Nagahama et al., 2001; Sohn et al., 2000). These studies ascribe an important role to several prefrontal regions as key parts in a distributed network also encompassing the posterior association cortices. For instance, mid-ventrolateral prefrontal cortex (BA 47/ 12) and anterior cingulate cortex (ACC; BA 24, 32) both have been found to become active in response to shift cues (Monchi et al., 2001). In contrast, dorsolateral prefrontal areas (DLPF; BA 9/ 46) become active in response to both shift and nonshift cues during WCST performance (Monchi et al., 2001) as well as during performance of other task-switching paradigms (Luks et al., 2002). Shift-related fMRI activation is also found at posterior parietal association cortex, which appears to work in cooperation with prefrontal cortex in the reconfiguration of task sets (Luks et al., 2002; Monchi et al., 2001; Rushworth et al., 2001; Sohn et al., 2000). On the whole, these studies are consistent with the idea that (1) ventral prefrontal regions support active comparison

of task-relevant information; (2) dorsal prefrontal regions are responsible for the monitoring of information during task switching; and (3) anterior cingulate regions are involved in conflict detection and management (Dreher and Berman, 2002; Monchi et al., 2001; Owen et al., 1996; Petrides et al., 2002; Stuss and Knight, 2002).

The actual time dynamics of activation within this prefrontal network are still poorly defined. Indeed, and in spite of a great interest for the functional fractionation of prefrontal cortex, so far there is little information about the temporal course of activation both within prefrontal regions and across with posterior cortical regions leading to a task switch. Most fMRI studies on set shifting (Konishi et al., 1998; Monchi et al., 2001) and task switching (Dreher et al., 2002; Luks et al., 2002) either did not provide information about the timing of activations across different brain regions or did not attempt to interpret any plausible differences between them (Dove et al., 2000; Dreher and Berman, 2002). It should be noted that such 'timeless' fMRI results implicitly favor a fully parallel model of prefrontal function, where apparently simultaneous activations at different areas of this frontal–posterior network seem to reflect several concurrently occurring switching operations. Such an entirely parallel neural model of task switching has been readily questioned by extensive behavioral evidence (Meiran et al., 2000; Pashler et al., 2001; Rogers and Monsell, 1995; Rubinstein et al., 2001; Ruthruff et al., 2001) and a few electrophysiological (Barceló et al., 2000, 2002; Rushworth et al., 2002b) and brain imaging studies (Monchi et al., 2001; Nagahama et al., 2001). These studies suggest at least two temporally well-segregated processing stages in task switching. Firstly, there is a task preparation stage that consists of task set reconfiguration or goal-shifting operations. Secondly, there is a task execution stage generally consisting of response selection operations such as response mapping or rule implementation (Meiran et al., 2000; Rubinstein et al., 2001; Ruthruff et al., 2001). In fact, some apparent inconsistencies about the role of prefrontal regions in task switching could be attributed to a failure of temporarily segregating these two distinct processing stages. Thus, when the task switch is self-paced (predictable), subjects may prepare for the next switch at any moment even before responding. For example, Meiran et al. (2000) have argued that when two tasks, A and B, shift with a fixed order (i.e., AABB...), participants need not wait to respond to the last Task A to prepare for the first Task B. Instead, they can prepare sooner, perhaps while executing the last Task A trial. Likewise, when a task cueing paradigm presents cue and target information simultaneously, it is difficult to temporarily isolate the brain activations related to the task preparation stage from those related to other task-switching stages such as stimulus identification, response selection, or movement production (Rubinstein et al., 2001). By considering a task preparation stage as temporarily distinct from a task execution stage in an unpredictable task-switching paradigm, we intend to clarify the relative involvement of different prefrontal regions in monitoring attentional control operations without the influence of target- or response-related processes. In addition, we expect that brain activation will also be temporarily organized both within prefrontal regions and across with posterior regions. For instance, the endogenous preparation for a task switch has been shown to involve earlier fMRI activation at lateral prefrontal cortex (BA 45/46), followed by later longer lasting activation at posterior association cortices (BA 40) (Nagahama et al., 2001; Sohn et al., 2000). However, with a temporal resolution of circa 2–3 s, these fMRI studies can hardly resolve the subsecond path of task-switching operations.

The excellent temporal resolution of electromagnetic brain signals could be used to improve our understanding of the brain dynamics underlying set shifting, both within prefrontal regions and across with posterior cortical regions. In this study, whole-head magnetoencephalography (MEG) was employed to explore the temporal pattern of neural activations associated with task set reconfiguration processes during the task preparation stage of WCST performance (Barceló et al., 2002). MEG is unique among other functional neuroimaging techniques for its ability to provide brain activation profiles of where and when activation occurs in the brain in relation to certain task events (Maestu et al., 2001, 2002, 2003b). To our knowledge, only one previous MEG study has assessed set-shifting operations using the WCST. Wang et al. (2001) reported higher magnitudes in the MEG signal in response to shift relative to nonshift cues at the DLPF cortex (BA 9, 10), the middle frontal gyrus (BA 9, 46), and the inferior frontal gyrus (IFG; BA 44, 45, 47). This differential pattern of activation was observed 460–640 ms relative to cue onset (i.e., during 'goal shifting'). Instead, two earlier peaks of MEG activation at 180–250 and 280–400 ms postcue onset did not differ across shift and nonshift trials, nor was there any distinct pattern of temporal activation across the aforesaid prefrontal areas. Taken together, the results of Wang et al. (2001) fall short of providing the fine-grained temporal analysis of activation either within prefrontal regions or across with posterior cortices. A number of methodological limitations may explain their relatively crude temporal analysis. On the one hand, MEG data were measured only from left hemisphere regions using a 37-coil magnetometer that had to be repositioned in separate experimental sessions. On the other hand, MEG data were collected separately for the cue and target periods in separate task sessions.

In the present study, equivalent current dipole (ECD) analyses of MEG activity sources were applied for a more sensitive spatiotemporal analysis of the brain dynamics during set-shifting operations. We focused on the cueing stage of our task rather than on potentially more complex response-selection processes taking place during the card-matching stage of WCST performance (Meiran et al., 2000; Pashler et al., 2001; Rogers and Monsell, 1995; Rubinstein et al., 2001; Ruthruff et al., 2001). Preparatory set-shifting operations can be explored when they are time locked to cues signaling unpredictable switches in task (Barceló et al., 2002; Ruthruff et al., 2001) and have the advantage of preventing motor contamination from the response stage of WCST performance. The purpose of the present investigation was to delineate the fast course of shift-related MEG activation both within prefrontal regions and across with posterior cortical regions. Our main working hypothesis was that shift cues would increase the number of MEG activity sources, as compared to nonshift cues, in those regions of interest (ROI) responsible for set shifting. We also predicted distinct temporal courses of MEG activation in those prefrontal and posterior association cortices specifically related to preparatory set shifting. According to the existing evidence, we expected earlier preparatory MEG activation at prefrontal areas devoted to conflict monitoring (i.e., ACC) and the manipulation of task-relevant information (i.e., IFG), followed by later activation at posterior association cortices involved in the retrieval and updating of task-set information (Barceló et al., 2002; Luks et al., 2002; Monchi et al., 2001; Nagahama et al., 2001).

Material and methods

Subjects

Sixteen right-handed participants (7 females and 9 males; mean age 26.4 ± 2.6 years, range 23–31 years) took part in the study. They had normal, or corrected to normal, visual acuity and no history of neurological or psychiatric disorder. Subjects gave informed consent for their participation. Three of these subjects had to be excluded from the analyses due to incorrect task performance (one subject) or excessive signal noise (two subjects). The behavioral and technical criteria for exclusion are explained fully below.

Stimuli and task protocol

Each trial began with the onset of a compound stimulus containing the four WCST key cards on top of one choice card, all centered on the computer screen. The stimuli were presented by an LCD video projector (SONY VPL-X600E) outside of the magnetically shielded room onto a series of in-room mirrors, the last of which was suspended 1 m above the subject's face. The cards subtended a visual angle of 4.6° horizontally and 3.5° vertically. Subjects were instructed to match the choice card with one of the four key cards following one of the three possible sorting rules: number, color, or shape of elements in the cards. The correct sorting rule was to be determined from auditory cues delivered randomly within 1000–2000 ms after each response, indicating whether to shift or to repeat the rule used previously (65 dB tones; 2000 Hz for nonshift cues, and 500 Hz for shift cues). Responses were made with a four-button panel (two buttons in each hand) in an array corresponding to the layout of the four key cards. A fixed intertrial interval of 1600 ms was adopted between cue onset and the onset of the next choice card (see Fig. 1). The task consisted of tree blocks of 36 series each. A WCST series consist of a variable number of card sorts ruled by the same sorting principle (i.e., color). The length of each series varied randomly between four and six trials including shift trials so that subjects could not predict the start of a new series. The minimum number of trials within a series was set at four trials given that in previous studies, neither RTs nor physiological measures showed any significant changes after the fourth trial within a classification series, thus suggesting a quick and efficient acquisition of the sorting rule (see Barceló et al., 2000, or Fig. 3 in Barceló et al., 2002). The order of the choice cards within the series was determined randomly. This task protocol used the 24 unambiguous choice cards of the original 64 WCST cards. Ambiguous cards are those that can be matched with a key card by two or more classification rules (i.e., a card with two red triangles can be matched with the first WCST key card—one red triangle—either by the color or the shape of elements in the card). Elimination of ambiguous cards is necessary for a sensitive scoring of set-shifting ability (see Barceló and Knight, 2002). At the beginning of each new WCST series, the subject needs to shift his or her task set and find the new sorting rule. An efficient series was scored if all three conditions were met that (a) the new task rule was not anticipated; (b) the subject found the task rule either in the second or third trial in the series; and (c) the task rule was not missed thereafter. Since the sorting principle changed randomly, subjects had to make a guess after the first

'shift' cue of a new series. An ideal subject had a 50% chance to choose the wrong sorting rule in the second trial of a new WCST series. These second trial errors were defined as 'efficient errors' whenever they involved a shift in rule and were followed by correct sorts in all remaining trials of that series. Therefore, only one first trial error and one second trial 'efficient error' were allowed in efficiently completed WCST series. Series with errors other than efficient ones were considered as 'failed series.' Failed series were not entered in the analysis of MEG activity but were considered in the comparisons of the behavioral accuracy across shift and nonshift trials. The average duration of each block was 18 min, including a 10-min rest period between blocks. Before the recording session, all subjects received a block of practice trials to make sure they had understood the instructions and could perform the task. This took less than 10 min or about 5–7 completed series. The same modified version of the WCST had been previously used to measure preparatory set-shifting processes with event-related brain potentials (Barceló, 2003; Barceló et al., 2002).

MEG recordings and data analysis

MEG recordings were carried out with a whole-head neuro-magnetometer (Magnes 2500®, 4-D Neuroimaging, Inc., San Diego, CA) consisting of 148 magnetometer coils. The instrument is housed in a magnetically shielded room designed to reduce environmental magnetic noise that might interfere with biological signals. The signal was filtered online with a band pass between 0.1 and 1 Hz (24 dB/octave attenuation), digitized for 700 ms (254 Hz sampling rate), including a 150-ms prestimulus period, and subjected to an adaptive filtering procedure that is part of the 4D neuroimaging signal analysis package. These steps are necessary to minimize the amount of low-frequency magnetic noise that is typically present in MEG recordings. MEG activation was obtained for shift and nonshift trials from efficient series only (i.e., see definition above). Shift trials were defined as the second and third trials after a shift cue (a 500-Hz tone). Nonshift trials were defined as those trials in efficient series where subjects received a 2000-Hz tone indicating to repeat the rule previously used. Since shift cues were less frequent than nonshift cues and to avoid task differences in the number of epochs used in computing the averages of MEG activation, the first nonshift trials within a series were not included in the averages. Trials containing eye movement or blink artifacts (as indicated by a peak to peak amplitude in the electrooculogram in excess of 50 μV) were also removed from the averaging procedures. A minimum of 80 ERF epochs were collected to calculate each individual waveform, with a mean number of 125.5 single shift trials and 147.1 single nonshift trials per subject (two subjects with less than 80 clean epochs had to be discharged from the study). Finally, the averaged epochs were digitally filtered with a low-pass 20-Hz filter (24 dB/octave attenuation).

The intracranial generators of observed ERFs (henceforth referenced to as activity sources) were modeled as single equivalent current dipoles (ECDs) and fitted at successive 4-ms intervals using the nonlinear Levenberg–Marquardt algorithm. For a given point in time, the ECD fitting algorithm was applied to the magnetic flux measurements obtained from a group of 34–38 magnetometers, always including both magnetic flux extremes. The ECD computation was restricted to latency periods during which a single pair of magnetic flux extremes dominated the left–

right or the anterior–posterior half of the surface. The algorithm used in this study searched for the ECD most likely to have produced the observed magnetic field distribution at a given 4-ms time interval. The ECD solutions were considered satisfactory only after meeting the following two criteria: (1) a correlation coefficient of at least 0.9 between the observed and the 'best' predicted magnetic field distribution; and (2) a goodness of fit of 0.9 or higher (Simos et al., 1999). To determine the anatomical regions where the activity sources were localized, ECD coordinates were overlaid onto T1-weighted magnetic resonance (MR) images (TR = 13.6 ms; TE = 4.8 ms; recording matrix 256 × 256 pixels; one excitation, 240-mm field of view; and 1.4-mm slice thickness) obtained in a separate session. The MEG-MRI overlay procedure has been described in detail elsewhere (Maestu et al., 2002).

Although a variety of source modeling approaches have been proposed, we decided to use a single-ECD source model that is part of the 4D neuroimaging software. Alternative algorithms hold many promises as tools for magnetic source localization but have not yet been validated against invasive localization procedures. In contrast, there is currently a wealth of data testifying to the validity of the single-ECD model for reliably localizing and lateralizing neurophysiological activity associated with cognitive functions (Maestu et al., 2001, 2002, 2003a,b; Papanicolaou et al., 1999; Simos et al., 1999). On the basis of this evidence, the single-ECD source model is part of the standard MEG analysis protocol in essentially all clinical applications. This source localization approach operates without a priori user-defined hypotheses regarding the location of the underlying activity sources. Visual inspection of the resulting activity sources localized in anatomically plausible brain areas was also taken into account.

Statistical analyses

A series of cortical regions of interest (ROIs) were drawn in individual MRI scans based on templates from a standard anatomical atlas (Damasio, 1995). Initially, these ROIs consisted of 17 cortical regions from each hemisphere including the anterior portion of the medial frontal gyrus (MFGa), the posterior portion of the medial frontal gyrus (MFGp), the anterior portion of the inferior frontal gyrus (IFGa), the posterior portion of the inferior frontal gyrus (IFGp), orbitofrontal gyrus (OrbG), anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), superior frontal gyrus (SFG), precentral gyrus (preCG), postcentral gyrus (postCG), superior parietal lobe (SPL), inferior parietal gyrus (IPG), supramarginal gyrus (SMG), superior temporal gyrus (STG), medial temporal gyrus (MTG), inferior temporal gyrus (ITG), and hippocampus (Hip). A three-way repeated measures ANOVA was applied to determine which of these ROIs showed significant differences in the number of activity sources associated with shift and nonshift task conditions. The three within-subject factors were as follows: task set (shift versus nonshift), hemisphere (right versus left), and ROI (17 cortical regions).

The temporal course of MEG activation was then further explored within those ROIs showing significant differences in the number of activity sources between shift and nonshift task conditions. Temporal MEG dynamics were examined by distributing the observed activity sources into six 100-ms latency bins extending from 100 to 700 ms postcue onset. Only relatively late activity sources were examined since 0–100 ms activity is thought to reflect early auditory processing (i.e., corresponding to M50 and M100 components) (Maestu et al., 2001, 2003a,b). A three-way

repeated measures ANOVA was used to explore the presence of a triple interaction between task set, ROI, and latency window. Specifically, this contrast tested for our second hypothesis about the existence of distinct temporal courses of MEG activation at those ROIs showing significant shift-related differences in activity sources in the previous main analysis. A series of a priori paired t tests were used to examine the predicted task differences at successive latency windows. A significance level of $P < 0.05$ was adopted for all main contrasts. A Bonferroni-corrected significance level of $P < 0.05$ was also adopted for all tests of simple effects involving multiple comparisons. Analyses were performed using the SPSS v10.0 software (SPSS Inc. 1999).

Behavioral shift costs were examined with an ANOVA with trials (position of errors within a series) as the repeated measures factor for the overall number of errors across WCST trials in failed series. Neither the first error from each new series ('first warning error'; Barceló and Knight, 2002) nor the 'efficient errors' from efficiently completed series were included in this analysis. The significance level of all ANOVAs was evaluated with the Huynh–Feldt (H-F) correction where appropriate, as a precaution against inhomogeneities in the variances of the means.

Results

Behavioral results

Subjects performed the task efficiently and typically committed less than 15% errors across all trials (except for one subject who had to be discarded from the analyses). The average percent of

Table 1
Mean (± SEM) number of MEG activity sources for shift and nonshift trials at each of the selected ROIs and corresponding P values for the difference between task conditions

ROIs	(Brodmann area)	Shift	Nonshift	P value
SFG	(6, 8, 9)	3.7 ± 1	3.9 ± 1.2	n.s.
MFGa	(9/46, 10)	7.9 ± 2.5	4.4 ± 0.2	n.s.
MFGp	(8, 8/9)	2.8 ± 1.2	2.2 ± 1.2	n.s.
IFGa	(45, 47/12)	5.3 ± 1.2	1.7 ± 0.6	0.01
IFGp	(44, 44/8/6)	5 ± 1.5	2.6 ± 0.8	n.s.
OrbG	(11)	5.3 ± 2.3	3.8 ± 1.5	n.s.
ACC	(24, 32)	11.4 ± 1.9	6.7 ± 1.4	0.01
PreCG	(4)	2 ± 0.7	2.6 ± 0.9	n.s.
SPL	(5, 7)	0.5 ± 0.4	0.7 ± 0.4	n.s.
IPG	(7/39)	2.8 ± 0.7	4.6 ± 1.2	n.s.
SMG	(40)	8.3 ± 2.2	2.8 ± 1.4	0.05
PCC	(23, 31)	1.5 ± 0.7	2.9 ± 1.1	n.s.
PostCG	(1, 2, 3)	2.5 ± 1.2	1.5 ± 0.7	n.s.
STG	(41, 42, 22, 22/38)	8.5 ± 1.7	14.7 ± 2.7	n.s.
MTG	(21, 21/37)	10.1 ± 2.8	9.8 ± 2.7	n.s.
ITG	(20, 20/38)	5.6 ± 1.5	3.8 ± 1.4	n.s.
Hip	–	9.9 ± 2	6.7 ± 1.7	n.s.

Note. SFG, superior frontal gyrus; MFGa, anterior portion of the medial frontal gyrus; MFGp, posterior portion of the medial frontal gyrus; IFGa, anterior portion of the inferior frontal gyrus; IFGp, posterior portion of the inferior frontal gyrus; OrbG, orbitofrontal gyrus; ACC, anterior cingulate cortex; PreCG, precentral gyrus; SPL, superior parietal lobe; IPG, inferior parietal gyrus; SMG, supramarginal gyrus; PCC, posterior cingulate cortex; PostCG, posterior central gyrus; STG, superior temporal gyrus; MTG, medial temporal gyrus; ITG, inferior temporal gyrus; Hip, hippocampus; n.s., nonsignificant differences; SEM, standard error of measurement.
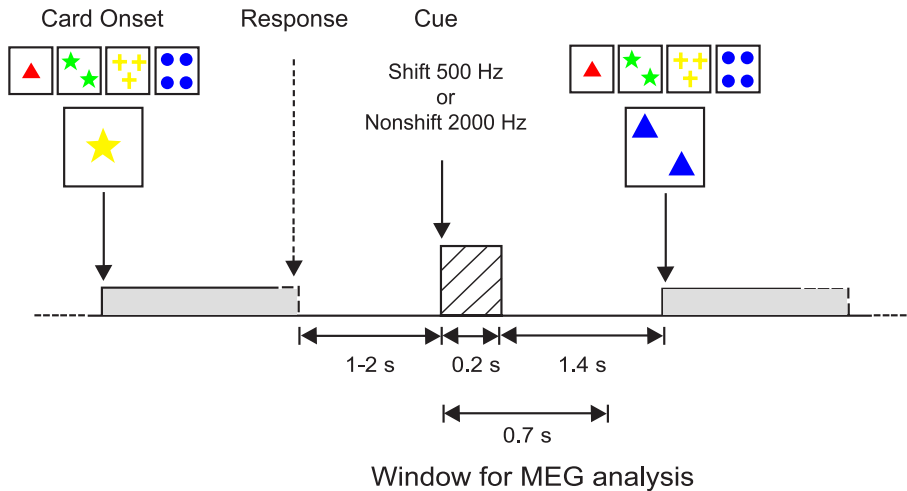
Fig. 1. Task design and window for MEG analysis. The sequence of events in a WCST series started with the onset of the choice card that could be unambiguously matched with one key card based on just one stimulus dimension. Card-matching stage: the choice card remained on display until a response was given. Cue stage: a 'shift' tone cued subjects to shift the task rule (sound frequency = 500 Hz). A 'nonshift' tone cued subjects to use the same task rule again (sound frequency = 2000 Hz).

efficiently completed series was 91.5% out of 108 series. The analysis of errors from failed series indicated that subjects were more likely to lose the task set at the beginning of a new series. Therefore, subjects committed more errors during the second ($P <$ 0.02) and third trials ($P <$ 0.007; Bonferroni-corrected values), as compared with the last trial in the series [$F(1,21) = 14.8$; $P <$ 0.0001; H-F = 0.4 for the main trial effect]. There were no differences in the number of errors committed between later trials in the series. The results confirmed the well-established costs in

response accuracy associated to task switching (Monsell, 2003; Rogers and Monsell, 1995; Rubinstein et al., 2001).

MEG results

Task-set switching, hemisphere, and ROI effects

A main task-set effect [$F(1,12) = 6.4$; $P <$ 0.027; H-F = 1] indicated that shift trials produced an overall larger number of activity sources than nonshift trials (mean ± SEM = 91.5 ± 6.4
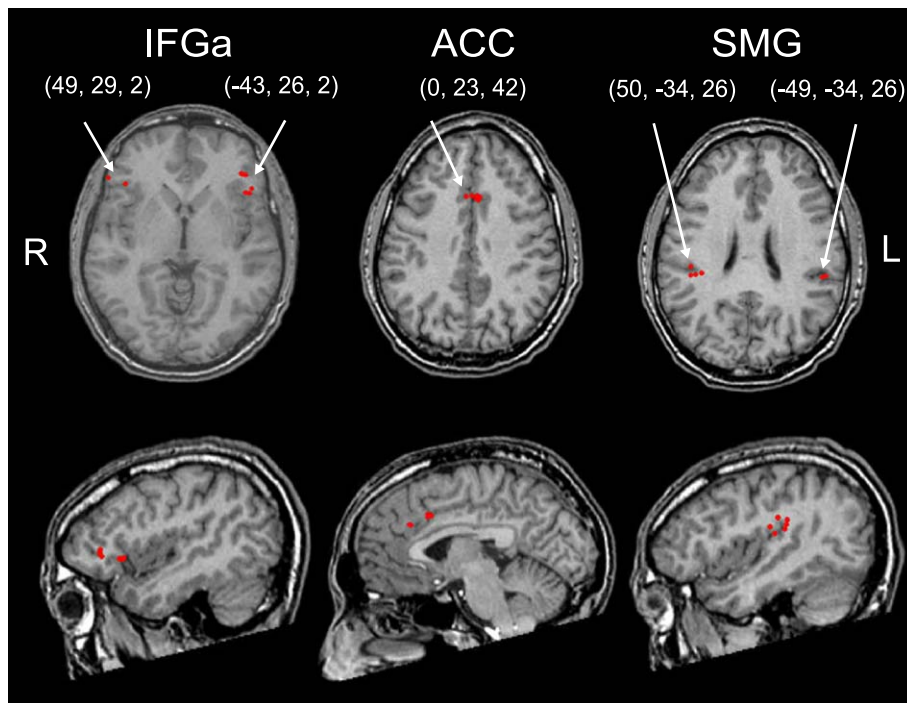

Fig. 2. MEG results for one representative subject. ECD solutions from the averaged event-related magnetic field are displayed overlapped with transversal and sagittal MRI scans. MEG activity sources are showed only for the three ROIs that reached significant differences between shift and nonshift task conditions: the anterior portion of the inferior frontal gyrus (IFGa) (left panel), the anterior cingulate cortex (ACC) (middle panel), and the supramarginal gyrus (SMG) (right panel). White arrows identify the Talairach–Tournoux coordinates of the clusters of activity sources at each of the ROIs.

versus 72.7 ± 3.1 for shift and nonshift trials, respectively). Moreover, a main effect for ROI [$F(16,192) = 6.5$; $P < 0.0001$; H-F = 0.3] as well as the interaction between task set and ROI [$F(1,12) = 2.0$; $P < 0.013$; H-F = 0.5] suggested that the predicted task-set differences in the number of activity sources varied across brain regions. Table 1 presents the results of a series of post hoc tests for simple effects to explore further the main interaction between task set and ROI (Bonferroni-corrected values). Only three ROIs showed a significant difference in the number of activity sources between shift and nonshift trials, namely, the anterior portion of the inferior frontal gyrus (IFGa), the anterior cingulate cortex (ACC), and the supramarginal gyrus (SMG) (see Fig. 2).

Task-set switching, ROI, and timing effects

The overall ANOVA performed on data across all six latency windows revealed a three-way interaction [task set × ROI × latency window, $F(9,114) = 1.98$, $P < 0.04$; H-F = 0.9], indicating temporal variations in the profile of task-related activation within the three selected ROIs. A series of a priori paired t tests were used to compare the temporal profile of MEG activation within the six latency windows postcue onset in the predicted direction. The anterior portion of the inferior frontal gyrus (IFGa) showed a trend
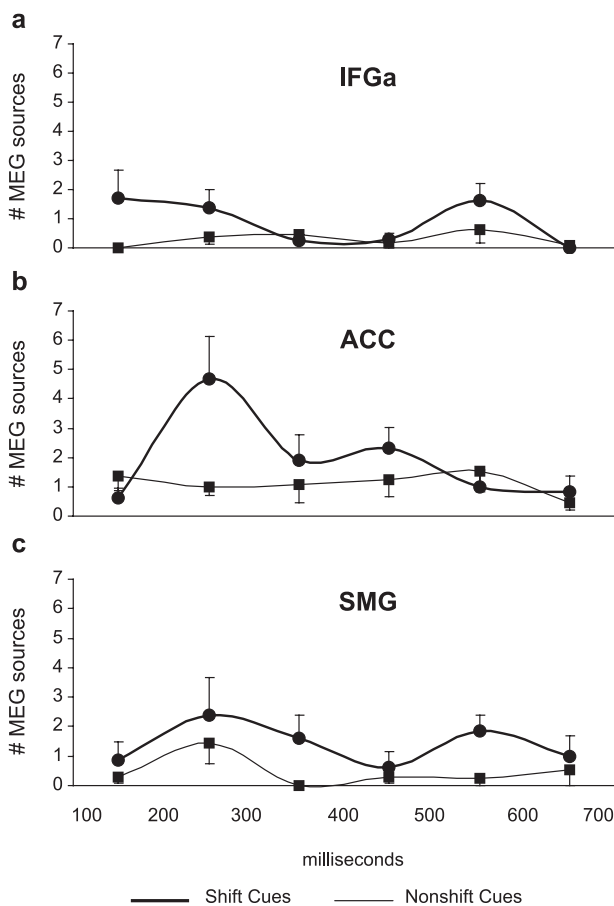
Fig. 3. Temporal course of MEG activation. Mean number of MEG activity sources in response to shift (thick line) and nonshift preparatory cues (thin line) at the three ROIs, which yielded significant differences between shift and nonshift trials: (a) the anterior portion of the inferior frontal gyrus, (b) the anterior cingulate cortex, and (c) the supramarginal gyrus. Vertical bars represent SEMs.

towards the expected task-set differences in the number of activity sources between 100–200 and 200–300 ms postcue onset [$t(12) = 1.72$, $P < 0.055$ and $t(12) = 1.7$, $P < 0.057$, respectively; see Fig. 3a]. Task-set differences reached significance [$t(12) = 2.89$, $P < 0.01$] when activity sources were collapsed in 200-ms time windows (i.e., from 100 to 300 ms). The anterior cingulate cortex (ACC) showed significant task-set differences in two separate time windows: 200–300 and 400–500 ms postcue onset [$t(12) = 2.64$, $P < 0.01$ and $t(12) = 2.41$, $P < 0.02$, respectively; see Fig. 3b]. The supramarginal gyrus (SMG) showed significant task-set differences in the two time windows composed between 300–400 and 500–600 ms postcue onset [$t(12) = 2.11$, $P < 0.03$ and $t(12) = 2.46$, $P < 0.02$, respectively; see Fig. 3c].

Discussion

To our knowledge, this is the first whole-head MEG study that explores the time course of preparatory set-shifting operations. We employed a modified version of the WCST to examine the spatiotemporal pattern of activation related to set-shifting operations triggered by shift and nonshift cues. Previous metabolic neuroimaging studies have suggested that this process depends on a distributed neural network encompassing prefrontal and posterior association cortices (Dove et al., 2000; Dreher and Berman, 2002; Luks et al., 2002; Monchi et al., 2001; Rushworth et al., 2001, 2002a; Sohn et al., 2000). Electrophysiological studies have grossly replicated these anatomical findings and have also provided a finer temporal analysis of large-scale neural network dynamics (Barceló et al., 2000, 2002). The present results help us to establish a clearer correspondence between recent fMRI and ERP research on the neural bases of set shifting in human subjects. Overall, there were a larger number of MEG activity sources during shift as compared to nonshift trials. Thus, 11 out of the 17 ROIs studied showed a larger number of MEG activity sources in response to shift cues as compared to nonshift cues, even though task differences reached statistical significance within only three of these regions (see Table 1). This activation was observed in a frontoparietal network of brain structures. Two prefrontal regions showed significantly larger number of MEG activity sources in response to shift cues as compared with nonshift cues: the inferior frontal gyrus (IFGa; BA 45, 47/12) and the frontomedial wall of the anterior cingulate cortex (ACC; BA 24, 32). At posterior regions, the largest shift-related increases in the number of MEG activity sources were found at the supramarginal gyrus (SMG; BA 40). As predicted by the second hypothesis, the analysis of the temporal course of activation within these regions revealed an early contribution from IFGa and ACC (circa 100–300 ms), followed by a later activation within SMG and ACC (circa 300–600 ms).

Anterior portion of the inferior frontal gyrus

Shift cues evoked a distinct pattern of activation within the anterior portion of the inferior frontal gyrus as early as 100–300 ms postcue onset. There is evidence from nonhuman primates that the midventrolateral prefrontal region (areas 45, 47/12), can exert a bidirectional top-down modulation of activity in post-Rolandic areas for the purpose of active comparison of stimuli held in working memory, encoding, and retrieval of information (Petrides

and Pandya, 2002). In human subjects, this ventral frontoparietal network has been proposed to act as a 'circuit breaker' of ongoing cognitive activity whenever a behaviorally relevant stimulus is detected. The activation within this area seems to be present whenever low frequency, unexpected, or previously learned relevant cues can break down the current task set and bring about a new one from the incoming information (Corbetta and Shulman, 2002). Luks et al. (2002) have provided an alternative interpretation about the functional meaning of the IFG activation during cue-related periods in similar task-switching paradigms. They reported significant activation within the IFG and the insula (BA 44/45) during both shift and nonshift cues, which was interpreted in relation to the operations of holding verbal task instructions in working memory and rehearsing them subvocally during the cue-target interval. Although, it seems reasonable to assume the presence of phonological processing during the cue-target interval, our results argue for the involvement of the IFGa during specific task-switching operations. The apparent inconsistencies across studies may be attributed to differences in the size of the defined ROIs (i.e., Luks et al., 2002, failed to distinguish between the anterior and posterior portions of the IFG and also included the insula within this ROI). Here a more precise anatomical analysis of the IFG allowed us to evidence a switch-related increase in the number of activity sources within the IFGa (BA 45, 47/12). In addition, our results show that the IFGp (BA 44, 44/8/6) was equally involved during both task set conditions, which might be taken as reflecting the phonological processing in working memory of shift and nonshift trial information (Poldrack et al., 1999). This later interpretation is consistent with the observation of a contribution of the IFGa in the initial stages of task switching and with previous fMRI results using the WCST (Monchi et al., 2001).

Anterior cingulate cortex

As expected, the anterior cingulate cortex (BA 24, 32) also showed a significant increase in the number of activity sources in association with shift cues. Task differences in MEG activation occurred within 200–300 ms and 400–500 ms postcue onset. Two alternative views have been proposed to account for ACC activation in Stroop-like tasks and task-switching paradigms. On the one hand, some authors have proposed that the ACC, together with other frontal regions, plays a key role in top-down attentional control. In their model of conflict monitoring, Carter et al. (1998, 1999) suggest that the ACC 'provides an on-line conflict signal, indicating the need to engage other brain regions to implement strategic processes.' On the other hand, some authors have emphasized the role of ACC in response-related processes such as conflict resolution, minimizing its involvement in the early phases of top-down modulation (Bunge et al., 2002; Milham et al., 2003; Paus, 2001).

Focusing our analysis on task preparation stage rather than on task execution processes allowed us to measure differences in activation between trials with different conflict demands, avoiding the influence of response-related processes. At the onset of a shift cue, the processing systems associated with the previous task must be overridden, while those associated with the new task must be activated. In consequence, there is probably greater competing activation from the 'inappropriate' task set for shift than for nonshift cues. Both conflict- and response-monitoring theories lead to opposite predictions about the likely involvement of the ACC in our task design. According to the conflict-monitoring framework, one would expect greater ACC activation for shift than for nonshift cues. On the contrary, according to the conflict-resolution theory, the ACC should be equally engaged by our shift and nonshift cues since cues in our task protocol did not demand a response nor could they be anticipated. In line with previous WCST (Monchi et al., 2001) and task-switching studies (Rushworth et al., 2002a), we found a bilateral increase in the number of activity sources within ACC during preparatory set shifting. These results can be viewed as supportive of the role of ACC in the executive control of attentional set shifting when activation of competing processing pathways occurs (Bush et al., 2000; Carter et al., 1998; Luks et al., 2002; van Veen et al., 2001). Nevertheless, it could be thought that the ACC could be monitoring conflict at different processing stages, in both cue- and response-related periods.

Supramarginal gyrus

Shift cues also elicited an increased number of MEG activity sources within the supramarginal gyrus (SMG; BA 40) during two time windows between 300–400 and 500–600 ms postcue onset. This spatiotemporal pattern of activation closely fits previous ERP results where the number of task sets in working memory during the preparatory stage of task switching modulated a conspicuous ERP response peaking 500–600 ms postcue onset over posterior association cortices (Barceló et al., 2002). This ERP response was originally interpreted as reflecting retrieval and updating of task rule information at posterior memory networks (Barceló et al., 2002). This interpretation is consistent with neuroimaging and lesion ERP studies demonstrating an SMG involvement in response to novel events and during the rapid retrieval and updating of task rules in working memory (Ardekani et al., 2002; Downar et al., 2000; Knight et al., 1989; Linden et al., 1999). Similar bilateral activation within the SMG and adjacent parietal associative cortices are engaged during preparatory cueing periods indicating a shift in set during both the WCST (Monchi et al., 2001), as well as other task-switching paradigms (Rushworth et al., 2001). Thus, the SMG activation observed in the present study might be related to the cue-driven retrieval and updating of task rules in working memory.

Other regions

MEG activation was also observed in other frontal, orbitofrontal, parietal, and temporal brain regions, although these activations did not statistically differ between shift and nonshift task conditions (see Table 1). The activity within these areas could not be specifically described as shift related. However, it seems reasonable to assume that these regions may be subserving more general cue-related operations necessary during both shift and nonshift trials. For instance, it is important to notice the activation over dorsal prefrontal regions (MFGa BA 9/46, 10), which have been proposed to be responsible for the monitoring of information in working memory (MacDonald et al., 2000; Petrides et al., 1993, 2002; Stern et al., 2000). Moreover, this finding fits with previous fMRI results indicating a common activation within the mid-dorsolateral prefrontal cortex (BA 9/46) during both shift and nonshift trials (Luks et al., 2002; Monchi et al., 2001).

Cue- and feedback-related or set-preparation processes?

Theoretical models of task switching have been normally based on simpler behavioral paradigms involving only two task sets. Thus, with only two alternating tasks, there is no doubt about which is the next correct task. When more than two tasks are used, then subjects are explicitly informed about the next task so as to eliminate any uncertainty from the task preparation stage (Rubinstein et al., 2001). On the contrary, the three task rules in the WCST force the subject to make a guess between two possible rules before shifting to one of them. That is, our subjects had to make a decision between two possible tasks before actually shifting to one of them. Whenever their first choice of task was 'incorrect' (which occurred by chance on 50% of the series and was followed by a second shift cue), they typically changed to the third remaining rule. This was a highly efficient process since normal subjects can easily keep track of the two discarded task rules to change to the remaining correct one. Moreover, there is absolutely no uncertainty involved after the second shift cue. The behavioral and physiological effects of uncertainty during these first versus second shift cues have been analyzed recently (Barceló and Knight, 2002; Barceló et al., 2000, 2002). Although longer RTs and larger posterior brain activation were found during the first (uncertain) as compared to the second (certain) shift cues in a series, either type of cues evoked similar brain responses over prefrontal regions (i.e., Barceló et al., 2002). Therefore, although our shift cues were not informative about which task should be performed next, this is not necessarily incompatible with the presence of set preparation processes. Surely, the fact that our subjects achieved over 90% correct series should be taken as an evidence of the existence of efficient preparatory processes prompted by the shift cues. Even in the absence of explicit cueing information about the next correct task, our subjects were able to keep uncertainty to a minimum and to prepare efficiently to perform the next task. The stage model proposed by Rubinstein et al., (2001) may account for at least part of the preparatory processes triggered by the shift cues in our task design. In line with these authors' view, upon hearing a shift cue our subjects must '...keep track of current and future tasks, inserting and deleting their goals in declarative working memory as needed...' (Rubinstein et al., 2001). In consequence, there are sound reasons to assume the existence of goal-shifting processes time locked to the onset of shift cues in our modified WCST task.

In the standardized version of the WCST, cues use to be feedback signals indicating 'right' or 'wrong' performance. In our modified version, feedback-related processes are minimized (see Barceló, 2003) since subjects were specifically told to consider the cues in terms of 'what to do next?' rather than 'how did I do before?' Thus, subjects were instructed to shift the task rule used in the previous trial upon hearing a shift cue and to repeat the rule upon hearing a nonshift cue. Nevertheless, future studies should compare the brain responses to switch trials from correct series and to negative feedback trials from failed series.

In conclusion, our MEG results provide support for the view that frontal cortex acts in concert with posterior association cortices during the preparation stage of set shifting. Shift cues elicited larger numbers of MEG activity sources than nonshift cues, and these were mainly observed in three frontoparietal regions. In addition, the analysis of the temporal dynamics within the examined ROIs showed a complex sequence in which the same regions became active at different moments in time. Thus, the use of brain imaging techniques with high spatiotemporal resolution could help to conciliate apparent inconsistencies between the putative role of regions like the IFGa and the ACC in set shifting. A tentative interpretation of the present results would regard the activation within the IFGa to reflect the earlier preparatory stages of set shifting. This is consistent with the proposed role of IFGa in breaking down an 'outdated' task set in response to behaviorally relevant sensory events. In addition, the subsequent pattern of activation closely fits prior neuroimaging and electrophysiological studies suggesting a role of ACC in the top-down modulation of posterior cortical regions like the SMG (probably involved in the updating of attentional templates for task rule information) at a moment when there is competing task information available. The present work provides a useful working hypothesis for subsequent studies about the temporal dynamics of set shifting, given that few brain imaging studies have attempted a comparison of the timing of activation across different brain areas. The overall correspondence of the present MEG data with those from previous fMRI and electrophysiological studies lent support to the utility of MEG for the study of complex cognitive processes such as the executive control of attention in combination with high spatial resolution techniques. Future research should clarify further the functional meaning of the temporal pattern of activation described here, as well as the specific contribution of the brain regions that were equally activated during both shift and nonshift trials.

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