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Four types of novelty–familiarity responses in associative recognition memory of humans

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Abstract

Animal studies show that, like inferior temporal neurons, dorsolateral prefrontal and parietal neurons often respond more strongly to individual novel than to individual familiar stimuli. It is currently unclear whether the novelty preference of prefrontal and parietal neurons extends to associative memory. We used electromagnetic recordings (MEG/EEG) and functional magnetic resonance imaging in two groups of healthy young adults to identify neural populations outside the inferior temporal cortex that exhibit associative novelty (stronger responses for new than for old configurations of two familiar items), and to distinguish them from associative familiarity (stronger responses for old than for new configurations of two familiar items). Subjects were required to learn and were later tested for associations based on the spatial configurations of two stimuli (a face and a tool). At test, learned (old) and rearranged (new) spatial stimulus configurations had to be discriminated. This recognition memory test could only be solved through the associative relationship between individual items because all component items of the stimulus configurations were equally familiar. In both imaging modalities, right dorsolateral prefrontal cortex and right parietal cortex showed an associative novelty response, whereas the right superior temporal cortex showed an associative familiarity response. With EEG/MEG only, the right extrastriate cortex showed an early associative familiarity and a late associative novelty response, whereas the opposite pattern emerged in bilateral frontopolar cortex. Thus, through a multimodal approach, it was possible to identify four types of associative novelty/familiarity responses outside the inferior temporal cortex.

Introduction

Neural populations in a number of brain regions can discriminate stimuli that have been recently encountered (old) from newly presented stimuli (new) thereby contributing to recognition memory in animals and humans (Ranganath & Rainer, 2003). When the new and old status of a stimulus is contingent upon the associative relationship between pairs of items rather than the presentation history of single items, the regions that are involved in the old/new discrimination also need to have associative coding properties. In humans, such properties have been observed in the medial temporal lobes (Badgaiyan *et al*., 2002; Düzel *et al*., 2003a), but associative novelty (stronger responses for new than for old configurations of two familiar items) and familiarity (stronger responses for old than for new configurations of two familiar items) responses have not yet been characterized in the prefrontal, parietal and lateral temporal cortices.

Animal studies suggest that prefrontal regions have associative coding properties, but thus far these have been demonstrated in working memory rather than in recognition memory tasks (Hasegawa *et al*., 1998; Rainer *et al*., 1999; Miller & Cohen, 2001). For instance, it could be shown that for a given cue, delay activity of prefrontal neurons in monkeys can represent an associated stimulus in a prospective manner (Rainer *et al*., 1999). However, whether prefrontal neurons can discriminate associatively new from associatively old stimuli and can thereby contribute to associative recognition memory is still unclear. A recent functional magnetic resonance imaging (fMRI) study of recognition memory in humans (Badgaiyan *et al*., 2002) failed to show associative novelty/familiarity differences in the prefrontal cortex. A recent event-related potential (ERP) study suggested that the right frontopolar region can distinguish between stimuli that are presented for the first time and stimuli that contain old items within 200 ms after stimulus onset (Tsivilis *et al*., 2001). However, the frontopolar ERPs in this study failed to distinguish between novel (rearranged) and familiar (studied) configurations of items.

To characterize the anatomical distribution and the timing of associative novelty and familiarity we analysed the sources of their respective MEG/EEG indices. EEG and MEG were co-recorded while nine subjects learned (over five repetitions) and were later tested for the association between a face and the location of an object (a tool). At test, learned (old) and rearranged (new) spatial stimulus configurations had to be discriminated. This recognition memory task could only be solved through the associative spatial relationship between individual items because at the time of recognition all component items were equally familiar. Thus, unlike in the Tsivilis *et al*. (2001) study, spatial relationship and not object identity distinguished learned from rearranged configurations. We have recently reported fMRI data obtained (in a different group of 11 subjects) with the same paradigm (Düzel *et al*., 2003a) demonstrating associative novelty and familiarity responses in hippocampal and parahippocampal regions. We will now consider the prefrontal, parietal and lateral temporal haemodynamic responses of that study to associative novelty and familiarity in order to validate the EEG/MEG source analysis presented here.

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Materials and methods

MEG/EEG experiment

Subjects

Nine volunteers were paid for their participation (five females, all right-handed according to self-report, mean age 23.2 years, SD 2.2). The study was approved by the ethics committee of Otto von Guericke University, Magdeburg, Germany and conformed with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Stimulus display

Stimuli consisted of pairings of grey-scale faces of people (head and shoulders looking straight ahead) with cartoon drawings of one of four tools (hammer, saw, screwdriver, wrench). Seventy such face–tool configurations were randomly assigned to each of two task conditions for each subject.

Design and procedure

Subjects studied, over five trials, the association between 10 faces and the spatial location of one of four tools. During the study phase, each face was presented for 4 s in the centre of a computer screen. Three seconds after the onset of face presentation, a tool appeared in one of the four corner positions of the screen and remained there for 1 s. This was followed by a 1-s ISI during which the stimuli were replaced with a fixation cross in the centre of the screen. On each trial, subjects were required to indicate the location of the tool prior to its appearance (after 3 s) by pressing one of four buttons (as subjects had not seen the pairings of the faces and locations of the objects on the first trial, they were instructed to guess and move their thumb). The face–location associations that needed to be learned and then discriminated during recognition could be best described as egocentric [egocentric (personal reference frame); allocentric (extrapersonal reference frame); Holdstock *et al*., 2000]. The reason why faces and tools were not presented simultaneously with the exception of the 1-s feedback period was to encourage the encoding of the faces and the tools or their locations as separate pieces of information that needed to be associated rather than components of a single compound stimulus (Sobotka & Ringo, 1993; Erickson & Desimone, 1999).

Following the fifth study trial, subjects received an associative yes/no recognition test. New test stimuli consisted of a studied face presented with its paired tool, but in a new location. Figure 1 depicts the scenario. Subjects were required to discriminate new stimulus configurations from old stimulus configurations. Note that the new test configurations consisted of highly familiar component parts: a previously viewed face and previously viewed tools; these stimuli were new only in the sense that an association between the face and the location of the tool had not been previously established. Each face–tool configuration was presented for 3 s with a 1-s ISI. During each recognition test, five old configurations were randomly intermixed with five new configurations.

This learning and recognition procedure was repeated 12 times, each time with a different set of 10 face–tool/location configurations.

Recording and analysis methods

MEG signals were recorded continuously from a 148-channel BTi Magnes 2500 whole-head magnetometer (Biomagnetic Technologies, San Diego, CA, USA), submitted to on-line and off-line noise reduction, filtered (IIR-Butterworth filter) with a bandpass from DC to 50 Hz, and digitized at 512 Hz. EEG signals were simultaneously recorded from 29 scalp electrodes. Eye blinks and eye movements were monitored via electrodes located on the infraorbital ridge of the right eye (referenced to the right mastoid) and the outer canthus of the left and right eyes (referenced to each other). EEG and EOG signals were amplified using a 32-channel Synamps amplifier (Neuroscan, El Paso, TX, USA) and co-registered with the MEG signals. Prior to recording, individual skull/scalp landmarks were digitized (left and right pre-auricular points, Cz, nasion, inion) using a 3Space Fastrak system (Polhemus, Colchester, VT, USA). The single-trial raw data underwent artefact rejection with an artefact threshold of 3.5 pT for MEG signals and 112.5 μV for EEG and EOG signals, and additional manual artefact rejection where necessary. A mean of 14% (SEM = 2.0%) of trials were rejected. The remaining trials were averaged and yielded ERPs from the EEG and event-related fields (ERFs) from the MEG. Based on previous EEG/MEG studies using recognition memory paradigms that required only a simple discrimination of old and new items (Düzel *et al*., 2001, 2003b), statistical analyses were confined to the data recorded from 200 ms prior to stimulus onset to 700 ms after stimulus onset. Within this time window, the signal-to-noise ratios of EEG and MEG data were expected to be sufficiently high (above 5) for source analysis (Düzel *et al*., 2003b).

Amplitude analyses of ERPs were performed on the basis of amplitude values obtained from two frontal (F3/F4) and two parietal (P3/P4) electrodes using serial related measures *t*-tests at every 4 ms (referred to as serial *t*-tests). Differences in amplitude were considered to be reliable if they were significant ($P < 0.02$) over at least 10 successive time points (40 ms). The time windows that showed significant differences were then further analysed topographically using ANOVA. For this analysis, mean amplitude measurements were normalized (over all electrodes) to remove confounding effects of the experimental manipulation (McCarthy & Wood, 1985) and four-way ANOVAs were conducted with the factors item-type (old vs. new), laterality (left, right) and position (frontal, parietal). All ANOVAs were carried out using the Greenhouse–Geisser correction for inhomogeneity of variance when applicable.

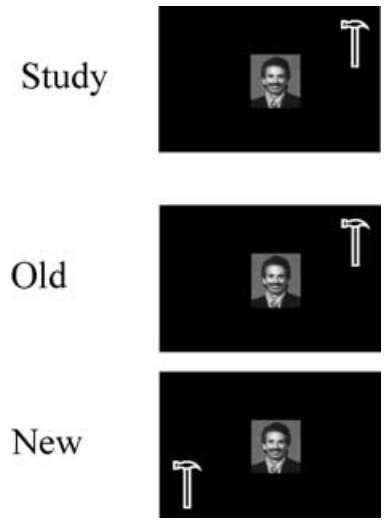


FIG. 1. This figure depicts the experimental paradigm. At study, subjects view a face paired with an object (one of four tools) in one of the four corner screen positions. Subjects are instructed to learn the association between the face and the spatial location of the object. Learning occurs over five trials. At test, subjects see either the original configuration or new configurations of the familiar stimuli. New configurations consist of the original face with the original tool in a new spatial location. Subjects are required to discriminate the new configurations from the familiar configurations by pressing a response key.

Source analysis

Methods for source analyses were adapted from Düzel *et al*. (2003a). Averaged EEG and MEG waveforms for correctly identified new and old configurations were used to localize the cortical generators using source analysis (CURRY, Version 4, Neuroscan, 2000) for each individual subject. A three-layer realistic head model (boundary element model, Hamalainen & Sarvas, 1989) was obtained from a segmented anatomical MRI scan (3D SPGR, spoiled gradient echo) of one of the participants. Current densities on the cortical surface were computed (the cerebellum was excluded to simplify the model, but might have contributed to the recorded electromagnetic activity) using the linear least-square minimum norm method (CURRY User Guide, Version 4, Neuroscan, 2000) after scaling EEG data with a conductivity factor (Düzel *et al*., 2003b). The conductivity factor was determined on the basis of a tangential dipole evoked by tactile stimulation of the index finger by an air puff at 30–40 ms latency in 16 subjects (Düzel *et al*., 2003b). Reliably across these subjects, the conductivity factor could be approximated to 0.8 and this value was used for all participants of the current study.

Current density distributions were computed every 4 ms for the time window from 0 to 700 ms after computing signal-to-noise ratios of EEG and MEG data in this time window with respect to the 200 ms baseline preceding stimulus onset (by 'noise' we mean neural activity in the baseline period that is allegedly uncorrelated with the old/new status of the stimulus). This analysis was performed separately for new and old stimulus trials. After source analysis, the cortex model with the current density distributions of each waveform was spatially normalized into the Talairach and Tournoux reference frame (Talairach & Tournoux, 1988). The current density distributions were then partitioned into 164 regions of similar size that evenly covered the entire brain volume, by summing up the current strengths of elementary dipoles in cortical regions with an average diameter of 2 cm. These final maps were used to visualize the cortical generators of waveforms and to assess significant differences in local source strength between old and new configurations across subjects with serial related measures *t*-tests every 4 ms (referred to as serial *t*-tests). The regions that were selected for serial *t*-test were restricted to the prefrontal cortex, the lateral temporal cortex and the parietal cortex. Differences in current strength were considered to be reliable if they were significant ($P < 0.02$) over at least 10 successive time points (40 ms) and over at least two neighbouring regions.

fMRI experiment

The experiment has been described in detail in Düzel *et al*. (2003a). Essential information is reproduced here for easier accessibility.

Subjects

Fifteen volunteers were paid for their participation. Because of technical difficulties involving stimulus presentation and data acquisition, data from 11 subjects (seven females, all right-handed according to self-report, mean age 24.6 years, SD 2.6) will be reported here. The study was approved by the ethics committee of Otto von Guericke University, Magdeburg, Germany and conformed with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Stimulus display

The stimulus display was the same as in the MEG experiment.

Design and procedure

Design, procedure and instructions were the same as in the MEG experiment with the following exceptions: (1) there were seven learning and recognition blocks in the fMRI; (2) during recognition testing there was a 12-s ISI in order to permit the BOLD response to return to baseline; (3) during the first learning trial, subjects were instructed to move their thumb (rather than press a button with their thumb) to indicate guessing because the fMRI-compatible response pad only contained four buttons.

Scanning and analysis methods

fMRI imaging was performed during the learning phase and during recognition testing with a GE 1.5 T Signa Neurovascular system using a standard quadrature head coil. Visual images were back projected onto a screen, which the subject could see through a mirror. Subject responses were given by magnet-compatible buttons. Conventional high-resolution structural images were acquired prior to functional imaging (T1 weighted rf-spoiled GRASS sequence). Each functional run during the recognition test consisted of 54 continuous whole brain volumes ($T2^*$ echo planar gradient echo sequence, TR 3 s, TE 40 ms, 30×5 gap 1 mm slices perpendicular to the hippocampal axis, field of view = 20 mm, matrix size = 64×64, voxel size = $3.13 \times 3.13 \times 6$ mm). Each subject except one (who contributed six) contributed seven study/test runs to the dataset.

Analysis was performed with SPM99 software (Wellcome, London, UK) after discarding the first four volumes to allow for stabilization of the BOLD signal. Each subject's functional volumes were: (1) corrected for differences in the acquisition times of different slices due to the interleaving of the slices; (2) realigned to their first scan in order to correct for movement; (3) spatially normalized to an EPI template (MNI reference brain; voxels were resized to $2 \times 2 \times 4$ mm); and (4) spatially smoothed (8 mm Gaussian kernel).

Statistical modelling for event-related design included all conditions of interest (old and new stimulus configurations) using a canonical haemodynamic response function for all event types. Subject-specific contrasts were estimated using a fixed effects model. For averaging across subjects, a second level analysis was performed using the individual contrasts in a random effects model. Results are reported in MNI coordinate system. For our interpretation of the MEG/EEG source results it was important to establish whether areas that displayed both a novelty and a familiarity response with MEG/EEG would show a haemodynamic difference between novelty and familiarity with fMRI. In order not to falsely conclude that there were no differences with fMRI, we chose a relatively liberal criterion of $P < 0.01$ uncorrected for multiple comparisons as an activation threshold.

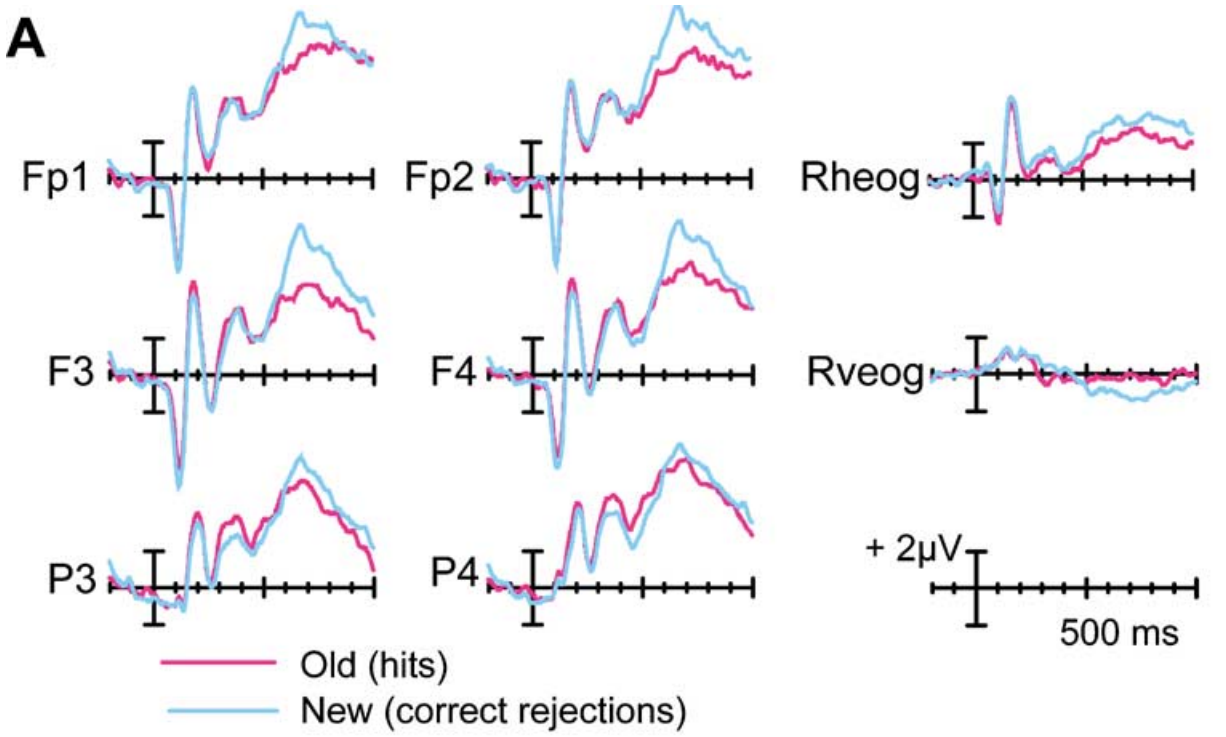
Results

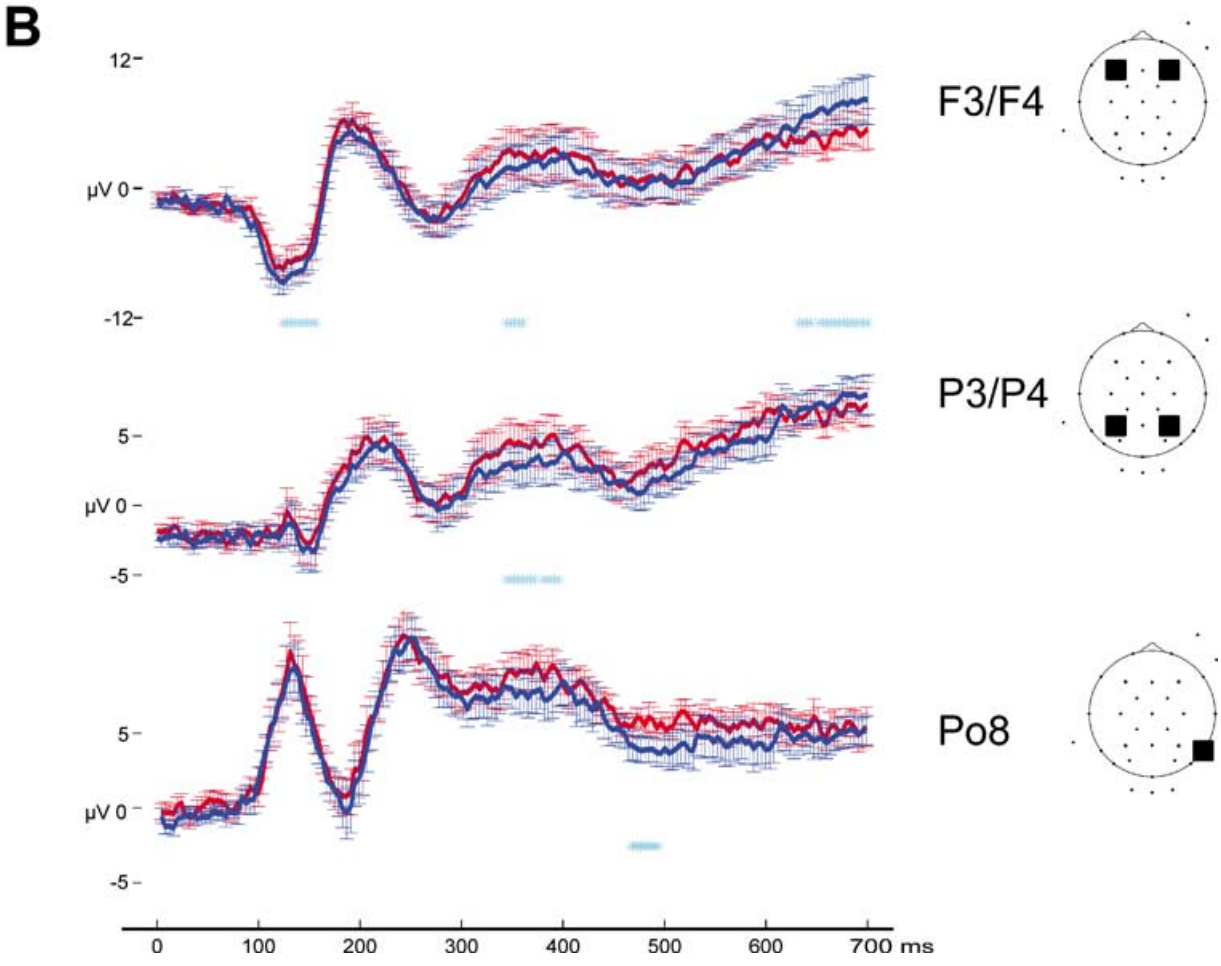
Behavioural results

MEG

Hit rates, false alarm rates (FA) and corrected recognition performance (hit – FA) showed that discrimination between new and old

FIG. 2. Grand average ERP and ERF waveforms. (A) Grand average ERPs for familiar (red lines) and new (blue lines) configurations. Fp1/2: left and right frontopolar electrodes; F3/4: left and right frontal electrodes; P3/4: left and right parietal electrodes. Rheog/Rveog: right horizontal and vertical ocular recordings. (B) Grand average ERPs for old and new configurations from bilateral frontal (F3/F4) and bilateral parietal (P3/P4) and right parieto-occipital (Po8) sites are displayed together with their standard error of the mean at every 4 ms. The stars indicate time points with significant differences in serial related measures *t*-tests at each time point. The schematic head drawing on the right illustrates the location of the electrodes from which the ERPs were obtained.


A
Fp1
Fp2
Rheog
F3
F4
Rveog
P3
P4
+ 2μV
500 ms
Old (hits)
New (correct rejections)


B
12
μV 0
-12
F3/F4
5
μV 0
-5
P3/P4
5
μV 0
-5
Po8
0
100
200
300
400
500
600
700 ms

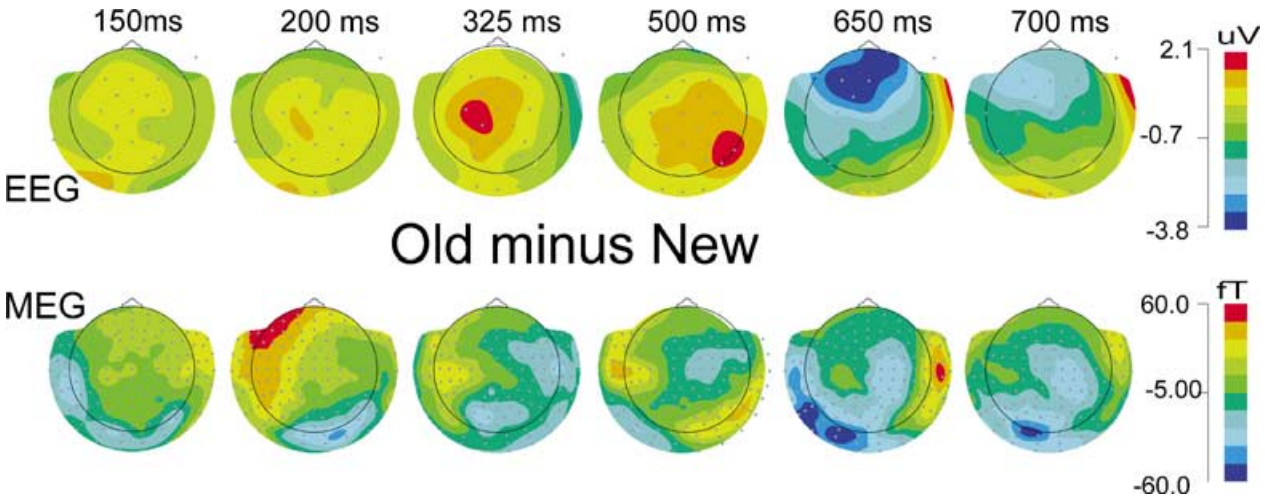


FIG. 3. Spline interpolated topographic maps of the grand average ERP (upper row) and ERF (lower row) difference between familiar and new configurations. Positive values (red colour) denote more positive ERPs or ERFs for familiar configurations and negative values (blue colour) denote more positive ERPs or ERFs for new configurations.

configurations was highly accurate (hits = 0.97; FA = 0.10; corrected recognition = 0.87). Reaction times could be analysed only for the fMRI data.

fMRI

Discrimination performance between new and old configurations in the fMRI was similar to performance in the MEG (hits = 0.94; FA = 0.06; corrected recognition = 0.88). Reaction times to correct recognition decisions (hits and correct rejections) were not different between hits (1820.34 ms) and correct rejections (1864.25 ms).

MEG/EEG

ERPs and ERFs

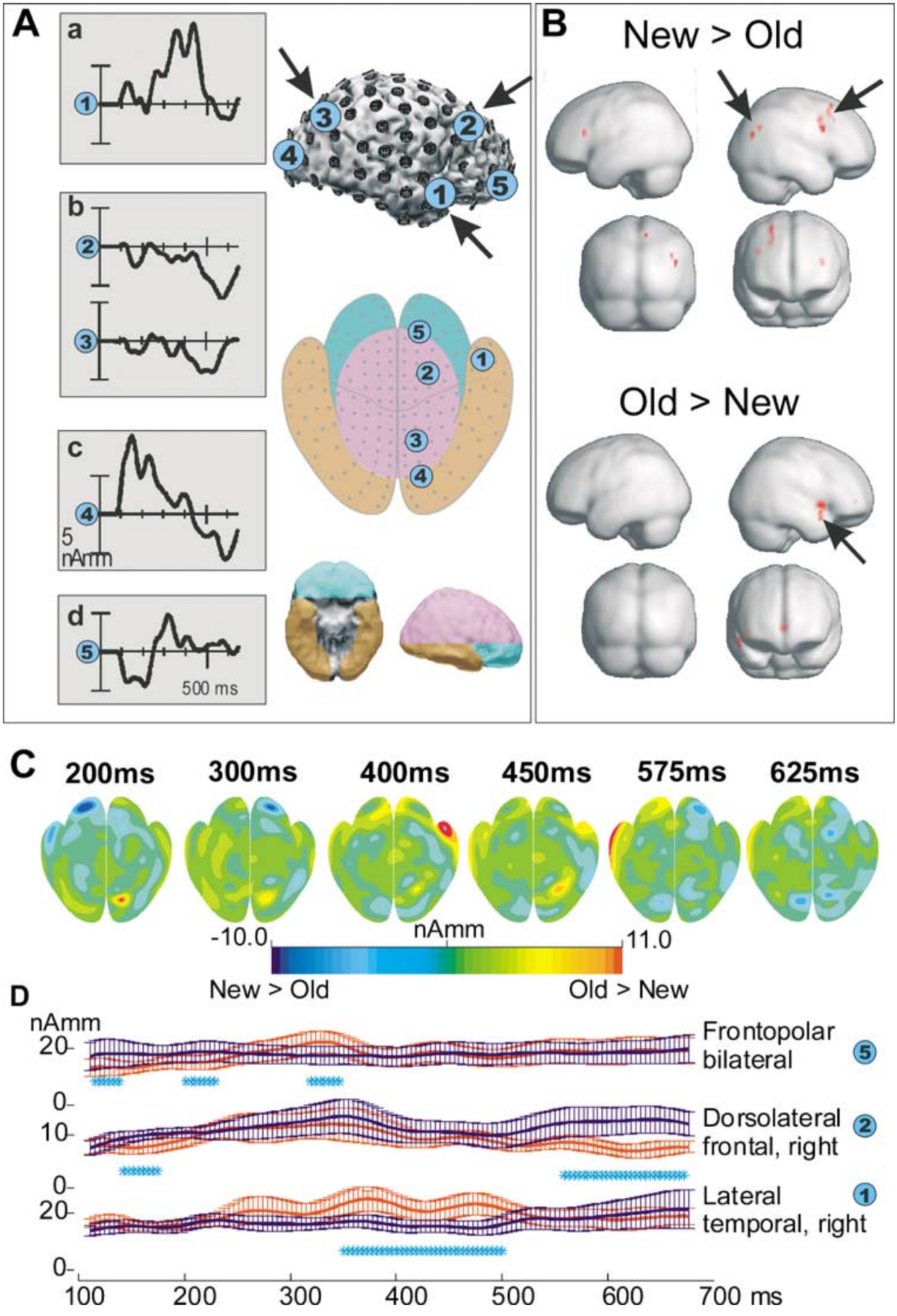
ERPs elicited by new and old configurations are displayed in Fig. 2A. Over frontal electrodes (F3 and F4), new configurations elicited more negative ERPs at 150 ms after stimulus onset. Over frontal and parietal electrodes, old configurations elicited more positive-going ERPs between 300 and 400 ms. This was followed by more positive ERPs for old configurations over left parieto-occipital electrodes between 450 and 550 ms. We therefore included the parieto-occipital electrodes into our statistical assessment. Then, again over frontal electrodes, new configurations elicited more positive-going ERPs than old configurations, between 550 and 700 ms. The frontal, parietal and right parieto-occipital ERPs with their respective standard error of the mean and the time windows with significant differences (serial *t*-tests) are illustrated in Fig. 2B. Figure 3 displays the topographical distribution of the ERP (upper row) and ERF (lower row) old minus new difference.

The topographical analyses revealed a significant item-type by location interaction between 125 and 175 ms ($F_{1,8} = 5.8$, $P < 0.05$) indicating the frontal location of the early old/new difference. Between 300 and 400 ms, there was no significant location by item-type or laterality interaction ($F_{1,8} = 5.1$, $P < 0.05$). Between 600 and 700 ms, there was a significant item-type by location interaction ($F_{1,8} = 7.1$, $P < 0.05$) showing that the late old/new effect was stronger over frontal electrodes. Between 450 and 550 ms, an additional ANOVA was conducted with electrodes Po7 and Po8 instead of P3 and P4 to account for the right parieto-occipital old/new effect. There was a significant item-type by location by laterality interaction ($F_{1,8} = 4.9$, $P < 0.05$) showing that the effect was largest over right parieto-occipital electrodes.

Source analysis

Mean signal-to-noise ratios in the first 700 ms after stimulus onset were 9.3 (SD 3.7) for hits and 9.8 (SD 3.1) for correct rejections in the MEG data and 11.4 (SD 3.8) for hits and 12.3 (SD 3.4) for correct rejections in the EEG data. The regions and their respective time courses of differences in current densities for new and old configurations [considered if differences were significant ($P < 0.02$) over at least 10 successive time points (40 ms) and over at least two neighbouring regions] are displayed in Fig. 4A, C and D. Examples for different patterns of source strength are displayed for old (red) and new (blue) configurations together with their standard error of the mean at every 4 ms in Fig. 4D. The stars indicate time points with significant differences in serial related measures *t*-tests at each time point. The topographic maps in Fig. 4C give a more complete overview of the

FIG. 4. MEG/EEG source analysis and fMRI results. (A) Differences in source strength (in nAmm) for familiar and new configurations. Positive values mean stronger responses for familiar stimuli and negative values mean stronger responses for novel stimuli. Each of the four grey shaded boxes exemplifies a typical response type. (a) Pure familiarity response, (b) pure novelty response, (c) early familiarity – late novelty response, (d) early novelty – late familiarity response. Numbers in blue circles indicate the location of the cortical region that showed the corresponding response. The locations are indicated on a 3D brain of one of the subjects that participated in the MEG/EEG experiment. The locations are also illustrated on a coloured, schematic flat map to ease the interpretation of the topographic maps in C. (B) Differences in haemodynamic response for familiar and new configurations. The upper four figures show stronger responses for novel stimuli and the lower four figures show stronger responses for familiar stimuli. Arrows indicate the regions that show corresponding results in the MEG/EEG data in A. (C) Current density reconstructions of the differences in source strength between familiar and new configurations. The current density maps are spline interpolations of source strength values (in nAmm) of 164 regions evenly distributed in Talairach space whose anatomical locations are illustrated on the figures in A [upper part: the 164 regions are indicated by circles on a single participant's brain; lower part: the circle marks the vertical level of the AC-PC line ($z = 0$), while the diagonal marks the horizontal level of the AC-PC line ($y = 0$)]. Red areas show stronger responses for familiar configurations and blue areas show stronger responses for new configurations. (D) Examples of different patterns of source strength are displayed for old (red) and new (blue) configurations together with their standard error of the mean at every 4 ms. The stars indicate time points with significant differences in serial related measures *t*-tests at each time point. The numbers in blue circles on the right refer to the same regions as in A.


A
a
b
c
d
5
nAmm
500 ms
B
New > Old
Old > New
C
200ms
300ms
400ms
450ms
575ms
625ms
-10.0
nAmm
11.0
New > Old
Old > New
D
nAmm
20
0
10
0
20
0
Frontopolar bilateral
5
Dorsolateral frontal, right
2
Lateral temporal, right
1
100
200
300
400
500
600
700 ms

current density differences between old and new configurations. Between 100 and 250 ms, new configurations were associated with higher current densities than old configurations over bilateral frontopolar cortex (left superior frontal gyrus, BA 10; *x*, *y*, *z* = 30, 70, 0; and the corresponding area on the left, Fig. 4A, C and D), whereas old configurations were associated with higher current densities over right extrastriate cortex (right middle occipital gyrus, BA 18; *x*, *y*, *z* = 10, −100, 30). Both regions showed opposite response types after 300 ms with current densities over frontopolar cortex being stronger for old configurations than new configurations and current densities over right extrastriate cortex being stronger for new configurations than old configurations. Regions that showed uniformly stronger responses for one stimulus category were the right dorsolateral prefrontal cortex (middle frontal gyrus, BA 8/9; *x*, *y*, *z* = 50, 20, 50; Fig. 4A, C and D) and right parietal cortex (precuneus, BA 39/7; *x*, *y*, *z* = 30, −70, 50) with stronger responses for new configurations from 550 to 650 ms, and the left anterior-lateral temporal cortex (superior and middle temporal gyrus, BA 38/21; *x*, *y*, *z* = 50, 10, −30, Fig. 4A, C and D) with stronger responses for old configurations from 350 to 500 ms.

fMRI

When the recognition of new configurations was compared with the recognition of old configurations (Fig. 4B), greater activity was noted in the right dorsolateral frontal cortex (superior and middle frontal gyrus, BA 6, x,y,z = 26 6 40, Z = 2.9, 493 voxels) and right parietal cortex (precuneus, BA 39 and 31, x,y,z = 38–66 32, and 18–52 28, Z = 2.76, 304 voxels). When the opposite contrast was performed (old configurations − new configurations), greater activity was noted in the right anterior-lateral temporal cortex (superior and middle temporal gyrus, BA 38/21, x,y,z = 54 6–20, Z = 3.5, 11 voxels), the right insula (BA 13, x,y,z = 42 8–4, Z = 3.6, 61 voxels) and anterior cingulate (x,y,z 0 50 0, Z = 2.8, 26 voxels).

Comparison of fMRI and MEG/EEG findings

MEG/EEG and fMRI data agreed best for those areas that showed a uniformly stronger response for either new or old configurations in the MEG/EEG, namely the right dorsolateral prefrontal cortex and the right precuneus. The location differences of the MEG/EEG and fMRI data are within the 2 cm inaccuracy limits that MEG/EEG source analyses can have (note that the coordinates given for the MEG/EEG source analysis results are in Talairach space while those for the fMRI findings are in MNI space). Areas that showed dual response patterns in the MEG/EEG with higher responses for new and old stimuli in different time windows did not reveal reliable activations in the fMRI contrasts of both stimulus types.

Discussion

MEG/EEG data from the first 700 ms after stimulus onset revealed four types of response patterns that discriminated between associative familiarity (stronger response to old configuration than to new configuration) and associative novelty (stronger response to new configurations than to old configurations). The first type of response was an associative novelty response only. This pattern was found in the right dorsolateral prefrontal cortex and the right parietal cortex (precuneus). The second type of response was an associative familiarity response only. This pattern was found in the right superior temporal cortex. The third and fourth types of responses were more complex in that they consisted of both associative novelty and associative familiarity responses within the same region, but either the associative novelty responses occurred earlier than the associative familiarity responses (bilateral frontopolar cortex) or the associative familiarity responses occurred earlier than the associative novelty responses (right middle occipital gyrus, cuneus, henceforth referred to as 'extrastriate').

The present data extend previous observations of a more strategic role of the prefrontal cortex in the discrimination of old and new information (Ranganath *et al*., 2000; Badgaiyan *et al*., 2002; Ranganath & Rainer, 2003). Recent fMRI and ERP studies had suggested that the anterior (Ranganath *et al*., 2000) and inferior (Badgaiyan *et al*., 2002) portions of prefrontal cortex are engaged when perceptually specific as opposed to general object information has to be used to discriminate old and new stimuli (Ranganath *et al*., 2000) or when relational as opposed single item information has to be used to discriminate old and new stimuli (Badgaiyan *et al*., 2002). Our data clearly implicate a direct participation of different portions of the prefrontal cortex in associative novelty and associative familiarity.

Two of the four associative novelty–familiarity response patterns were visible with both MEG/EEG and fMRI. Areas that showed pure associative novelty and pure associative familiarity in the MEG/EEG data also produced a reliable haemodynamic difference in the fMRI contrast of new and familiar configurations. Areas that showed a mixed associative novelty–familiarity response in the MEG/EEG measures, on the other hand, did not produce a significant haemodynamic contrast. One possible explanation is that an area that showed both an associative novelty and associative familiarity response did not produce a significant haemodynamic difference in the fMRI because the haemodynamic response integrates neural activity across both response components. Relying solely on fMRI in the current study would have concealed the mixed associative novelty and associative familiarity responses of the frontopolar cortex and the extrastriate cortex. That one and the same region can display both an associative novelty as well as an associative familiarity response in different time windows is not surprising. Similar phenomena of coexistence of different response types within the same region have been reported before for working memory (Quintana & Fuster, 1999; Fuster, 2001; Rainer & Miller, 2002).

The earliest associative responses emerged at about 150 ms after stimulus onset. Early responses were visible in both ERPs (Figs 2B and 3) and in the source analysis results (Fig. 4A, C and D). According to the source analysis results the orbitofrontal cortex showed an associative novelty response at about 150 ms, while the extrastriate cortex showed an associative familiarity response in the same time window. The ERPs revealed only a frontal difference in this time window, presumably reflecting the frontal component of the source analysis results. The source analysis pattern is remarkable in two ways. First, the early timing of the effects show that by about 150 ms after stimulus onset the associative relationship between a pair of items is analysed to a level sufficient for prior history of presentation to influence their associative neural processing. Second, it shows that already at this early time window, neural populations in frontopolar cortex are preferentially affected by stimulus configurations that are new, whereas in extrastriate cortex they are preferentially affected by stimulus configurations that are old. This dissociation argues against a common mechanism such as priming to underlie early effects of configural stimuli in general. Rather, there appears to be a regionally specific early response to configural stimuli suggesting that these early responses go beyond simple facilitation of processing. It is therefore likely that these early responses already index processes that contribute to recognition memory judgements.

The functional and anatomical mechanism that make possible the similar early timing of the orbitofrontal associative novelty and the extrastriate associative familiarity effect are unclear at the present time. One possible hypothesis is that both areas receive projections from a common third region, and are not sequential stages of an

associative memory network. It is, for instance, known that inferior temporal neurons can distinguish old and new stimuli as early as 100 ms after stimulus onset (Brown & Xiang, 1998). Furthermore, output from inferior temporal regions is redistributed, via feedback projections, to much of the neocortex including early visual cortex (Rockland & Van Hoesen, 1994; Lavenex & Amaral, 2000) and to the orbitofrontal region (Rempel-Clower & Barbas, 2000) via feedforward projections. These redistributed connections terminate in the superficial layers of their neocortical targets (Lavenex *et al*., 2002), which makes it likely that ensuing changes in local field potentials evoked at these terminals will be picked up with MEG/EEG. As for the orbitofrontal novelty response, the assumption that it might reflect feedforward projections from the inferior temporal cortex is further supported by findings that fronto-temporal disconnection diminishes prefrontal novelty responses (Parker & Gaffan, 1998; Parker *et al*., 1998; Rainer & Miller, 2002).

A recent ERP study of configural memory for item pairs (Tsivilis *et al*., 2001) described early frontal old/new effects at about 200 ms, but unlike the present study these differences emerged between stimuli that entailed at least one studied component item and stimuli that consisted of entirely new items that had not been studied before in the experiment. In the same study, no significant ERP differences were observed between old and new configurations of studied items. There are some critical experimental differences that might explain why we found an early associative frontal old/new effect here and why it was absent in the Tsivilis *et al*. (2001) study. First, in our study, the difference between old and new configurations was task-relevant, whereas in the Tsivilis *et al*. (2001) study this difference was task irrelevant. Second, in the Tsivilis *et al*. (2001) study, objects were presented in one of four corners of a computer screen at study but at the centre of the computer screen at test. Hence, both the old and new configurations in the Tsivilis *et al*. (2001) study had a spatial rearrangement in them. Third, the type of rearrangement that distinguished old and new configurations in the Tsivilis *et al*. (2001) study was based on object-identity rather than on spatial location as in our study. Finally, in our study, subjects learned each configuration over five trials and received feedback after each learning trial. Study lists consisted of 10 item pairs only. In contrast, in the Tsivilis *et al*. (2001) study, the study list consisted of 144 item pairs. Therefore, discrimination between old and new stimuli was approximately 10% higher in our study.

There is considerable evidence from ERP studies that have used single item recognition memory paradigms that amplitude differences between correctly recognized old items and correctly rejected new items are related to different forms of recognition memory (Mecklinger, 2000). A frontocentral, mid-latency (300–500 ms) old/new difference has been related to familiarity-based recognition, whereas a late (500–800 ms) left parietal old/new effect has been related to recollection-based recognition memory (Düzel *et al*., 1997, 2001; Curran, 2000). One influential suggestion concerning the neural underpinnings of these two ERP indices of recognition memory is that the later effect reflects retrieval from episodic memory and is critically dependent on the hippocampal formation, whereas the earlier is a non-episodic form of memory for which the hippocampus is not critical (Rugg *et al*., 1998; Mecklinger, 2000; Düzel *et al*., 2001). In our study, we have also observed a midlatency, centrally distributed difference between old and new configurations that was followed by a later right parieto-occipital difference (Figs 2 and 3). Whether these two old/new differences are qualitatively compatible to the midlatency fronto-central familiarity effect and the late parietal recollection effect of single item recognition memory experiments remains speculative. If so, this finding would be compatible with our recent fMRI observation that the difference between old and new configurations can also be coded by neural populations that are not held to be primarily responsible for episodic memory, such as the parahippocampal cortex (Düzel *et al*., 2003a). By that token, the present ERP results might provide additional support for the notion that neural codes of associative recognition memory are not restricted to the episodic memory system.

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Abbreviations

ERF, event-related fields; ERP, event-related potential; FA, false alarm rates; fMRI, functional magnetic resonance imaging.

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