7. Proprioceptive Evoked Potentials (PEP) in Man: Cerebral Responses of Changing Weight Loads on the Hand

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We studied cerebral proprioceptive evoked potentials (PEP) in 10 subjects elicited by a change in weight load of 400 to 480 g on the right hand. The cortical activation of the PEP was triphasic C3’/P70, N130, P190, and biphasic Fz/N70, N150 components. Statistical analyses indicated significant contralateral activation, C3’ vs C4’ (P70, t = 4.34, p < .002; N130, t = 3.65, p < .005; P190, t = 3.10, p < .02), and significantly larger frontal than parietal activation, Fz vs Pz (N70, t = 8.89, p < .001; N150, t = 5.45, p < .001). The deflections of the PEP resemble the suggested reafferent activity in the movement-related potential and the EP seen when inducing a long-latency stretch reflex, making it likely to be attributable to muscle afferent activity. PEP could be used in the investigation of sensory–motor integration and perception.

Little is known of the processing of proprioception in the human brain. If electrical stimulation is used for EP generation, the natural temporal pattern of deep receptor firing is largely abolished and the felt sensation is highly artificial and does not resemble any kind or combination of natural receptor activity. Our objective was to examine information processing of the temporal aspects as opposed to the spatial aspects of a proprioceptive stimulus. We decided to explore a natural quality of proprioception—appreciation of applied force—by scalp recordings of proprioceptive evoked potentials (PEP).

Our aim was to make a natural signal for the integrated sensory–motor system and follow the cortical activation associated with its perception. A natural event such as change of hand-held load always activates both cutaneous and muscle stretch receptors and elicits a compound proprioceptive evoked potential. To generate an evoked potential the stimulus was very brisk resulting in an unfamiliar sensation best described as “the feeling of carrying a basket of apples when another apple is suddenly thrown into it.” The sense of effort or perceived heaviness has been suggested to emerge from motor efferent activity in combination with afferent feedback of all types. Muscle afferents have a direct pathway to motor cortex, as established in studies of monkeys, and this feedback probably is the afferent part of the long-latency stretch reflex (Abbruzzese, Berardelli, et al., 1985; Goodin, Aminoff, et al., 1990).

Differential modulation or “gating” of the electrically elicited somatosensory evoked potential (SEP) by passive and active displacement and tactile stimuli has been consistently demonstrated. This implies that as we use a compound natural stimulus, it is not possible to know how the temporal pattern of the arrival of the different afferent volleys will affect the cortical activation. Thus the instruction to subjects was to have a sustained isometric stiff wrist and a relaxed grip, yielding that
the slight attention and the stimulus importance as a proprioceptive signal would enhance the intermediate–late-latency EP.

Ten right-handed male healthy volunteers aged 24–35 years gave informed consent in accordance with the Helsinki declaration. Silver/silver chloride cup scalp electrodes were placed according to the International 10–20 System at FP1, FP2, Fz, Cz, Pz, C3', and C4'—the last two placed 2 cm posterior to C3 and C4—referenced to bilateral earlobes. EOG were recorded to facilitate artifact rejection. EEG signals were amplified 50,000 times with a frequency pass band of 1–280 Hz. Sampling rate was 1 kHz. All electrode impedances were below 5 kOhm. EMG was recorded from disposable 3M electrodes 3 cm apart on m. extensor carpi radialis longus in four subjects. EMG was recorded at a sample rate of 1 kHz, with a bandpass of 1–200 Hz.

The subject, eyes closed, had his pronated right forearm in a horizontal armrest holding a plastic handle carrying a static load of 400 g. The hand was supported to the level of the metacarpophalangeal articulation of the thumb. An additional load of 80 g was applied through a nylon wire connected to the handle and a servomotor driving a reel. The change of weight had a linear increment of 20 g/10 ms. The maximum increment lasted 100 ms. Interstimulus interval was 2 s and each run consisted of 120 identical stimuli. All subjects had four runs during a 4-h session.

EMG was rectified and EEG was baseline adjusted to the mean of the last five prestimulus sample points. Averaged epochs of 1 s (−400 to 600 ms) were time locked to stimulus onset trigger. The EP consists of an across day average of four runs after offline visual inspection and removal of artifact contaminated blocks. Mean number of included blocks in the individual EP was 405 trials (range 254–467). Only the first run was averaged for the EMG.

The grand average demonstrated an intermediate latency and significant but low-amplitude EP (see Fig. 1), comparing to the prestimulus baseline. All subjects dis-
played EP activation. Seven subjects had evident activity both at the contralateral and the frontal sites. Two subjects did not show the contralateral activation and one subject did not demonstrate the frontal activation. Cortical activation manifested as a triphasic waveform (denominated by approximate latency) with a mean onset of 37.7 ms at C3’ and a biphasic waveform at Fz. At C3’, P70 (significant difference from baseline peak positivity, $t = 3.16, p < .01$), N130 (no significant difference from baseline peak negativity), and P190 (significant difference from baseline peak positivity, $t = 1.28, p < .03$). At Fz, N70 (significant difference from baseline peak negativity, $t = 4.67, p < .01$) and N150 (no significant difference from baseline peak negativity). In the individual EPs we saw a small bifurcation negativity in the middle of C3’ P70 in six subjects. The EMG showed a phasic activation with a mean onset latency of 42 ms and a mean peak latency of 70 ms.

We found significant contralateral activation effect on amplitudes in response to right hand stimulation, C3’ vs C4’ (P70, $t = 4.34, p < .002$; N130, $t = 3.65, p < .005$; P190, $t = 3.09, p < .02$), and significantly larger frontal than parietal activation, Fz vs Pz (N70, $t = 8.89, p < .001$; N150, $t = 5.45, p < .001$). This clearly indicates that a fast change of a hand-held load can elicit an EP without the change of position usually involved in EPs elicited by passive movements.

The W-waveform of the proprioceptive EP at C3’ looks very much like the earlier recordings of mechanically induced somatosensory EPs of passive movement, magnetic muscle stimulation, and stretch (Abbruzzese, Berardelli, et al. 1985; Goodin, Aminoff, et al. 1990) even though the diversity of recording sites and stimulation techniques make it difficult to compare directly. On the other hand cutaneous SEPs elicited by mechanical skin compression, by passive movements, or by electric stimulation of superficial nerves feature an early negative peak resembling the N20 of the median nerve SEP.

In the recordings of a proprioceptive stimulus, a passive flexion of the PIP joint of the right middle finger (Mima, Terada, et al., 1996), no W-waveform was displayed at C3, but the poststimulus recording was only 100 ms. The cutaneous input due to superficial receptors of changing touch location was minimized by the handle being in a stable grip position, but deep cutaneous pressure sensors were probably activated both in the palm of the hand and along the contracting muscle bellies of the forearm resting on the support.

The delayed onset latency of our EP could be due to the simultaneous stimulation of a great part of the upper extremity and the many afferents involved of different conducting velocity. A minor W-waveform is embedded in the C3’ P70 in accord with the bifurcation we saw in six subjects, which means that this deflection could be a compound of the activity recorded in median nerve SEPs as P40 and P100. The later contralateral N130 is not significantly different from baseline but resembles closely the N140 of median nerve SEP (Desmedt, Huy, et al., 1983). It is mirror imaged by a positive deflection in the frontal leads. As the long-latency stretch response has been considered specifically related to situational set, posture, and limb stiffness (Goodin, Aminoff, et al., 1990) we expected it to be induced by our experiment. The EMG activity we recorded with an onset latency of 42 ms is probably a long-latency stretch response, even though it was not preceded by an evident early spinal stretch reflex. This could be due to the isometric condition as this has been shown to selectively enhance the long-latency response.

The prominent frontal negative deflection—N70—in our recording could be similar to the frontal negativity evident in passive movements EP in N45 (Mima, Terada, et al., 1996) and N130 (Tarkka and Hallett, 1991) and in stretch elicited EP in N110 (Goodin, Aminoff, et al., 1990) and N75 (Abbruzzese, Berardelli, et al., 1985) at Cz or frontal contralateral recordings. Our frontal N70 and the negativity of passive movements (Mima, Terada, et al., 1996) may possibly share the same generator as the
frontal N30 of the median nerve SEP. It could reflect activity of the mesial supplementary motor area, primary motor cortex, or the net sum of multiple generators. The long-latency stretch response would then be the efferent part of a semiautomatic sensory–motor integration that we see reflected in the central frontal negativity. In one study of the movement-related potentials (MRP) the frontal negativity was very similar in the corresponding passive movement, but no contralateral positive deflection was seen and it was proposed that supplementary motor area was involved in the generation of the frontal negativity (Tarkka & Hallett, 1991). Our N70 may be generated by the same processes as these passive or active movement-related potentials.

We conclude that a brisk change of a hand-held load elicits an EP resembling the suggested reafferent activity in the MRP and the EP seen when provoking a long-latency stretch response. This makes us assume that muscle stretch afferent activation is the main contributor to this proprioceptive EP. Proprioceptive EPs could be useful for the investigation of aspects of natural sensory–motor integration and perception and of the cognitive processing of somatosensory information. Thus it could be of clinical relevance in neurological diseases like parkinsonism, tic disorders, and infarcts of the cerebellum as well as in neuropsychiatric disorders like schizophrenia.

REFERENCES


8. Distinction between Item-Related and Task-Related Brain Activity in Episodic Encoding: A Psychophysiological Investigation

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Event-related potentials were recorded while young adults participated in episodic encoding tasks and passive viewing tasks with random shapes or words. We analyzed the data by dissociating task-related activity from item-related activity. First, we found a larger direct-coupled (DC) shift in the left anterior frontal sites in verbal encoding, but not in nonverbal encoding. We confirmed that episodic encoding does not involve preferentially the left prefrontal regions irrespective of the type of material. Second, the topographies of the N400 and LPC components differed according to the type of material in the encoding tasks, but not in the viewing tasks. Thus, an interaction between material properties and task instructions determined the item-related activity. We conclude that encoding should be regarded as the outcome of multiple processes. © 2001 Academic Press
The HERA (hemispheric encoding/retrieval asymmetry) model postulates that the left prefrontal cortical regions is preferentially involved in the encoding of novel information into episodic memory, whereas the right prefrontal cortical regions is preferentially involved in episodic memory retrieval (Tulving et al., 1994). Further studies have shown that this model is valid regardless of the type of material (Desgranges et al., 1998). However, some exceptions have been reported to the HERA model. Brewer et al. (1998) noted a right frontal activation during the encoding of nonverbal material, such as complex scenes. Thus, the leftward lateralization in encoding may depend on both encoding strategies and type of material. Moreover, the HERA model is essentially based on studies using positron emission tomography and functional magnetic resonance imaging. Due to the lack of studies using the high temporal resolution technique, it is unclear whether the leftward activations reflect either the item-related or the task-related processes. This ambiguity might be resolved through the use of event-related brain potentials (ERPs). Indeed, as a result of its high temporal resolution, ERPs allow for discrimination between neural networks of item and task. Coupling event-related potentials and positron emission tomography, Duzel et al. (1999) found that the right prefrontal cortex activation may be linked to maintenance and manipulation rather than item-related processes in episodic retrieval. In the current study, we examined the electrophysiological activity and left prefrontal lateralization involved in episodic encoding with regard to task processes and type of material within the same participants. ERP waveforms were obtained from sufficient scalp sites in order to investigate whether different experimental conditions engage functionally dissociable cognitive processes.

Method

The tasks were run on a computer monitor screen. Participants performed two tasks (memory, passive viewing) which were crossed with the type of items (random shapes, words).

Participants. Eight healthy young students (four females; mean age 21 years) were recruited from the University of Montreal. All participants were right-handed. None were taking medication or had conditions that could affect the nervous system.

Materials and procedure. The nonverbal material consisted of complex random shapes, and the verbal material was composed of nouns (four to five letters). All stimuli were unique. Encoding in episodic memory was evaluated by using lists of 16 items that were to be memorized. For each type of material, there were 10 lists of items to memorize, divided in two blocks. After the memorization of each list of items, there was a recognition phase. The instructions were to memorize the items in order to recognize them after. In the nonverbal passive viewing task, participants were asked to view the random shapes, and for the verbal passive viewing task they simply had to read the words without additional task demands. For each type of material, seven lists of 16 items were used. For both the encoding and the passive viewing tasks, the items were presented successively in the center of the monitor, each one for a duration of 1000 ms. The interstimulus interval was 2500 ms. In order to elicit the task processes, the instructions also appeared on the screen for 5000 ms prior to the presentation of each list.

EEG was recorded from 56 tin electrodes embedded in an electrocap. Recording locations were based on the guidelines for standard electrode position by the American EEG Society. The montage included eight midline sites (Fz, Cz, Pz, Oz, Afz, FCz, CPz, POz) and 24 sites over each hemisphere (left/right: F1/F2, F3/F4, F5/F6, F7/F8, AF3/AF4, FC1/FC2, FC3/FC4, FC5/FC6, C1/C2, C3/C4, C5/C6, CP1/CP2, CP3/CP4, CP5/CP6, T7/T8, FT7/FT8, TP7/TP8, P1/P2, P3/P4, P5/P6, P7/P8, PO3/
PO4, PO7/PO8, O1/O2). All electrodes were referenced to linked earlobes and their impedance was kept below 5 kOhm. The electrooculogram (EOG) was recorded using four 9-mm tin external electrodes. For the horizontal EOG, electrodes were placed at the outer canthus of each eye, and for the vertical EOG infra- and supraorbital to the left eye, in line with the pupil when looking straight ahead. A bioelectric amplifier model ISS3-32BA (SAI–InstEP), amplified the EEG signals (Gain $\pm 3500$ for the EOG and $\pm 10,000$ for the EEG) with a bandpass between 0.02 and 30 Hz.

In order to examine item-related activity, ERPs were averaged with temporal window of 200 ms until 1500 ms after the stimulus onset. To investigate the task-related activity, ERPs were recorded using the direct-coupled (DC) technique and averaged on 500 ms before, until 9500 ms after a stimulus onset. Statistical analysis on ERPs was performed using ANOVA (with the Greenhouse–Geisser correction when applicable) applied on baseline-to-peak amplitudes of the N400 (300–500 ms) and LPC (450–700 ms) for item’s ERPs. For task ERPs the absolute area under the curve was taken from 2000 to 9300 ms poststimulus. Due to our interest in the laterality effect, we focused on lateralized sites and the areas in which the components are most clearly defined. For both N400 and LPC, components were picked up over the frontal (AFs and Fs), frontocentral (FCs), and centroparietal (Cs and CPs) regions. For large windows, the studied electrodes were anterior frontal (AFs and Fs).

**Results**

Accurate performance on the subsequent yes/no recognition memory test was used as an indicator for successful encoding. Words were better recognized than random shapes (respective percentages of hits, 85 and 60%). A Student’s $t$ test revealed that this difference was significant ($p = .001$). All subjects responded above the chance level.

**Item-related activity.** For encoding tasks, the three-way ANOVAs with Material (random shapes, words), Laterality (right hemisphere, left hemisphere), and Site (nine levels) on N400 amplitudes revealed that the greater amplitudes for words than random shapes was more pronounced on frontocentral sites than on the anterior sites [Material $\times$ Site, $F(8, 56) = 8.31, p = .000$]. The Laterality by Site interaction was also significant [$F(8, 56) = 2.68, p = .014$]. On LPC, the amplitudes were larger for random shapes than for words in the central and centroparietal regions than in the frontal and frontocentral regions [Material $\times$ Site, $F(12, 84) = 7.49, p = .001$]. The ANOVAs on N400 peak latencies indicated a Condition by Laterality interaction [$F(1, 7) = 8.64, p = .02$], which reflected shorter latencies in the right hemisphere for random shapes (mean, 398 ms) than for words (mean, 427 ms), whereas the difference between the materials was less pronounced for the left hemisphere (respectively, means, 411 and 405 ms). On LPC peak latencies, there were no significant effects. For the passive viewing tasks, due to the lack of N400 consistency, the ANOVA was not conducted. On the LPC amplitudes and latencies, only the Laterality by Site interactions were significant [respectively, $F(12, 84) = 2.33, p = .01$; and $F(12, 84) = 2.28, p = .01$].

**Task-related activity.** For nonverbal material, the ANOVA [Condition (encoding, passive view) $\times$ Laterality (right hemisphere, left hemisphere) $\times$ Site (3 levels)] revealed that visual perception was associated with a sustained positive DC shift that was topographically maximal over the left anterior frontal electrodes, whereas for the recognition the DC shift was identical in both the right and the left anterior frontal electrodes [Condition $\times$ Laterality, $F(1, 7) = 7.42, p = .03$]. The Laterality by Site interaction was also significant [$F(2, 14) = 4.01, p = .04$]. For verbal material, the Condition by Laterality interaction revealed a trend toward significance [$F(1, 7) =$
showing a DC shift more pronounced in the left hemisphere in verbal encoding than in the reading. The Condition by Site interaction was also significant \( [F(2, 14) = 4.53, p = .03] \). The significant effect of Condition showed that the DC shift was more pronounced in encoding than in reading \( [F(1, 7) = 10.15, p = .01] \). The DC shift was more significant in the left than in the right anterior frontal sites \( [\text{Laterality effect}, F(1, 7) = 5.53, p = .05] \).

Discussion

Our findings revealed a sustained DC shift that was more pronounced in the left anterior prefrontal regions during verbal encoding than in reading, whereas the DC signal was similar for the hemispheres during nonverbal encoding. Using an ERP paradigm to dissociate task-related effects, we confirmed that the left prefrontal regions are preferentially involved in episodic encoding irrespective of the type of material (Brewer et al., 1998). Further, the task-related hemispheric asymmetry was different from that of item-related asymmetry. We did not find left frontal superiority for verbal material when comparing the type of material for encoding tasks in which item-related activity was evaluated through the use of high-level processing components such as N400 or LPC. Finally, the item-related activity seems to be determined by the interaction between properties of the materials and task instructions, since the N400 and LPC amplitudes and their topographies varied according to material and condition. In sum, encoding should be conceptualized as the outcome of interacting processes, such as task-related processes, material-related processes, and item-related strategies that are dependent on task demands.

REFERENCES


9. The Neural Basis of Interference Resolution: Manipulations of Interference

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The goal of this experiment was to investigate the neural basis of interference resolution within WM through separate manipulations of WM load and interference in Sternberg’s Item Recognition paradigm. We acquired whole-brain fMRI data for eight young volunteers while they performed blocks of four different Item Recognition trial types: Load1 (Baseline), Load4 Low Recency (LR), Load4 High Recency (HR), and Load6. Both the load manipulation and,
A critical function of working memory (WM) is the ability to suppress irrelevant or no-longer-relevant information. This ability, referred to as ‘inhibition’ or ‘interference resolution,’ is profoundly impaired in humans and animals with prefrontal damage. Little is currently known about the neural mechanisms underlying interference resolution.

The goal of the present experiment is to investigate the neural basis of interference resolution within WM through separate manipulations of WM load and proactive interference in Sternberg’s Item Recognition paradigm (Sternberg, 1966; Monsell, 1978; Jonides et al., 1998; D’Esposito et al., 1999). We reasoned that if interference and load manipulations were to have similar effects on brain activation, this would suggest that an increase in interference might be functionally equivalent to an increase in load. Alternatively, if increased interference were to place more demands on different brain regions than increased load, this would provide support for the idea that interference resolution is a distinct process operating within WM.

We acquired whole-brain fMRI data for eight healthy young volunteers (ages 19–32 years; three F, five M) while they performed alternating blocks of four different Item Recognition trial types: Load1 (Baseline), Load4 Low Recency (LR), Load4 High Recency (HR), and Load6. Both the load manipulation and, to a lesser extent, the interference manipulation resulted in slowing of response times (164 and 65 ms, averaged across positive and negative trials). As expected, slowing in the interference condition occurred primarily on negative trials, for which subjects were on average 114 ms slower to respond in the interference condition. On these trials, the probe did not appear in the current target set but appeared in the immediately preceding target set, creating conflict between the familiarity of the item and its relevance to the current trial.

Although subjects were both slower and less accurate on Load6 than Load4 HR
trials, the interference manipulation was associated with greater brain activation than the load manipulation in a number of brain regions, including dorsolateral prefrontal and anterior cingulate cortices (see Fig. 1). These results suggest that interference resolution involves specific prefrontal circuits that cannot be accounted for simply by WM task difficulty.

REFERENCES


10. Involvement of Prefrontal Regions on Episodic Retrieval: Evidence for a Generate–Recognize Asymmetry Model

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Using positron emission tomography (PET), we compared the involvement of different regions of the prefrontal cortex (PFC) on four episodic retrieval tasks: item recognition, context recognition, word-stem cued recall, and associative cued recall. Before each scan, subjects studied a list of words or word pairs, and during the scan, they performed one of the tests. The results indicated that left PFC activity was greater for recall than for recognition tests, whereas right PFC activity was greater for recognition than for recall tests. This pattern is consistent with a generate/recognize asymmetry model (GRAM), which proposes that left PFC is differentially more involved in generation processes than is right PFC, whereas right PFC is differentially more involved in recognition processes than is left PFC.

Introduction

Episodic memory refers to the encoding and retrieval of personally experienced past events. In the laboratory, episodic memory is typically investigated by exposing subjects to series of items, such as words or faces, and subsequently testing their memory with recall or recognition tests. According to generate–recognize models, recall tests require the production of candidate items (generate) followed by the selection of candidates with appropriate contextual tags (recognize). In the case of recognition tests, the first process is bypassed because the candidate items are provided by the experimenter. In the present positron emission tomography (PET) study, we investigated the contribution of different regions of the prefrontal cortex (PFC) to generation and recognition processes in episodic retrieval.

In functional neuroimaging studies, PFC activity during episodic retrieval tends to be right-lateralized (e.g., Nyberg, Cabeza, & Tulving, 1996), but left PFC activations are commonly found. One possibility is that they reflect semantic retrieval oper-
ations during episodic retrieval performance (Nyberg et al., 1996). For example, Cabeza et al. (1997a) suggested that the left PFC activation displayed by old adults during cued-recall reflected the generation of candidate responses. If left PFC is differentially involved in the generation process, right PFC could be differentially involved in the recognition process. We call this hypothesis the generate–recognize asymmetry model or GRAM. An alternative account is that left PFC activations during episodic memory retrieval mediate more systematic and reflectively complex retrieval processes, whereas right PFC activations mediate more heuristic and reflectively simple operations. This hypothesis is known as cortical asymmetry of reflective activity or CARA (Nolde, Johnson, & Raye, 1998).

In the present PET study, we contrasted predictions of GRAM and CARA. We scanned subjects during four different episodic retrieval tasks (see Fig. 1a): item recognition (IRN), context recognition (CRN), stem-cued recall (SCR), and associative-cued recall (ACR). We performed two main contrasts: (1) SCR/ACR vs IRN/CRN and (2) ACR/CRN vs IRN/SCR. GRAM predicts a dissociation of PFC activity in the first contrast: left PFC should be more activated for SCR/ACR, which involve generation, than for IRN/CRN, which depend primarily on recognition, whereas right PFC should show the converse pattern. In contrast, CARA predicts a dissociation in the second contrast: left PFC should be more activated for ACR/CRN, which depend on complex systematic operations, than for IRN/SCR tasks, which depend on simple heuristic processes, whereas right PFC should show the opposite tendency. The most critical test of CARA is a contrast between IRN and CRN, because they entail the largest difference in complexity for the same kind of materials (single words): left PFC should be more activated for CRN than for IRN, whereas right PFC should show the converse pattern.

**Method**

**Subjects.** Twelve right-handed healthy young adults (mean age 25.3 years, SD 4.1).

**Materials.** Each study list consisted of 24 target words (or word pairs in ACR) plus one primacy and two recency fillers. IRN consisted of 14 studied words plus 10 nonstudied lures (4 before, 2 during, and 4 after the scan window). SCR consisted of the three-letter stems of the 24 targets. ACR consisted of the first word of each of the 24 pairs. Finally, in the CRN condition, 12 targets were presented auditorily and 12 targets were presented visually, and for the test, the 24 words were presented visually.

**Procedure.** Subjects were PET scanned while performing each of the four tests. The presentation rate at study was 3 s/item, except in the IRN condition, in which it was 750 ms/item to decrease overall performance. In the four retrieval tests, low and high performance conditions were produced by repeating the study once or four times, but for the present analyses we averaged across this manipulation. At test, words were presented for 4 s followed by fixation for 1 s. The test list started 30 s before and continued 30 s after the 60-s scan window. In all conditions, subjects responded to each item by saying one word aloud: “old” or “new” in IRN; the word recalled in ACR and SCR; and “seen” or “heard” in CRN. If subjects could not make a decision or recall a word before fixation appeared, they said “pass,” so that one word was spoken in every trial. In the baseline scan, subjects read numbers written in text (“one,” “two,” etc.) every 5 s.

**PET methods.** Nine scans were conducted: two in each retrieval condition and one in the baseline condition. The baseline condition was always scan 5, and the four retrieval conditions were counterbalanced across scans. Each word list was asso-
FIG. 1. (a) Classification of the four episodic retrieval tests investigated according to the generate–recognize distinction (columns) and according to CARA (rows). (b) Contrast between recall (SCR/ACR) and recognition (IRN/CRN) tests. (c) Contrast between complex (ACR/CRN) and simple (SCR/IRN) episodic retrieval tests.
associated with one scan, so list assignment was counterbalanced along with test order. PET scans were obtained using a bolus injection of $^{15}$O--H$_2$O. PET data was re-aligned, normalized, and smoothed (10 mm) using SPM99b. An activation was considered significant if it had at least 10 voxels above $Z > 3.09$ ($p < .001$ uncorrected).

Results

Behavioral results. The proportion of correct recall was .75 in ACR and .71 in SCR. The proportion of correct recognition in CRN was .87, which adjusted for chance is equivalent to .74. In IRN, there were .76 hits and .07 false alarms, yielding a corrected recognition score of .69. In ANOVA on corrected performance, the main effect of test was nonsignificant, suggesting similar levels of episodic recovery in the four tests.

PET results. Consistent with GRAM, the SCR/ACR vs IRN/CRN comparison (see Fig. 1b) yielded a clear dissociation in the lateralization of PFC activity. Left PFC (Area 45/46) was more activated for SCR/ACR than for IRN/CRN, whereas right PFC (Areas 9 and 46/10) showed the converse pattern. This dissociation could be also observed in pairwise comparisons. Left PFC activations were found in ACR-IRN, ACR-CRN, SCR-IRN, and SCR-CRN, whereas right PFC activations were found in IRN-SCR, IRN-ACR, CRN-SCR, and CRN-ACR. Inconsistent with CARA, the SCR/IRN vs ACR/CRN comparison (see Fig. 1c) did not yield a clear lateralization pattern. In the ACR/CRN-SCR/IRN contrast, frontal activity was nonsignificant. In the SCR/IRN-ACR/CRN comparison, there was a small activation on right PFC (Area 44). Most importantly, in the critical contrast between CRN and IRN, the former was associated with bilateral PFC activations (right Area 9, left Area 45/46) and the latter with a left PFC activation (Area 9). Thus, in disagreement with CARA, left PFC was more activated for IRN than for CRN.

Discussion

In summary, the present study provided evidence supporting GRAM: left PFC activity was greater for recall than for recognition tests, whereas right PFC activity was greater for recognition than for recall tests. By contrast, the results were inconsistent with CARA. This view predicts that left PFC activity should be greater for the more complex ACR and CRN than for the simpler SCR and IRN whereas right PFC activity should show the converse pattern. Neither of these results was clearly found. Moreover, left PFC was more activated for IRN than for CRN.

The finding that left PFC was more active for recall than for recognition whereas right PFC was more active for recognition than for recall is consistent with previous functional neuroimaging data. The PET study by Cabeza et al. (1997b) did not find differences in PFC activity between recall and recognition, but it employed a word-pair recognition test that could involve a generation component. The results of a second PET study comparing recall and recognition (Rugg et al., 1998) are consistent with the present findings. Compared to baseline, a left PFC area was activated in recall but not in recognition, whereas in a high-target-density condition, a right PFC area was more activated for recognition than for recall. Frontal lesions usually produce larger deficits on recall tests than on recognition tests. This finding is not incompatible with the present results, because in most neuropsychological studies, recall has been more difficult than recognition and, hence, more sensitive to brain damage.

Memory deficits after PFC lesions are most noticeable in recall and context memory tests. However, lesion data have not provided clear evidence about whether recall and context memory depend on the same or different PFC regions. The present study
is probably the first neuroimaging study to directly compare recall and context memory, and it suggests that left PFC is more involved in recall than context memory whereas right PFC shows the converse pattern.

In conclusion, the present study provided evidence for a generate–recognize asymmetry model (GRAM), which proposes that left PFC is differentially more involved in generation processes than is right PFC, whereas right PFC is differentially more involved in recognition processes than is left PFC.

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11. Dissociating the Contributions of DLPFC and Anterior Cingulate to Executive Control: An Event-Related fMRI Study

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Both DLPFC and the anterior cingulate (ACC) show increased activation during executive control; however, the specific contributions of each area remains controversial. Two classes of processes underlie control. Strategic processes provide top-down support for task operations; evaluative processes monitor ongoing performance. Using event-related fMRI and a task-switching Stroop paradigm we examined whether the strategic/evaluative distinction could be used to dissociate DLPFC and ACC. LDLPFC showed cue-related activity which was greater for color naming than word reading, with greater activation correlating with smaller Stroop effects ($r = -0.63$). ACC showed only response-related activity which was greater for incongruent color-naming trials and correlated positively with the RT Stroop effect ($r = 0.41$). These data suggest DLPFC contributes a strategic function and ACC an evaluative one to executive control. © 2001 Academic Press

Executive control encompasses a broad class of mental operations involved in initiating and maintaining controlled information processing and coordinated actions. These include strategic processes, which provide top-down support for task appropriate behavior, and evaluative processes, which monitor ongoing behavior and signal when strategic processes need to be more strongly engaged. Neuropsychological and functional neuroimaging studies suggest that two regions of the frontal cortex, dorsolateral prefrontal cortex (DLPFC), and anterior cingulate cortex (ACC) are active when executive control is engaged. Both regions of cortex have been hypothesized
to play a key role in providing top-down support for task-appropriate behavior (D’Esposito et al., 1995).

However, recent work using electrophysiology (Ghering et al., 1993) as well as studies using event-related fMRI have suggested that the ACC serves a performance monitoring function, rather than a direct role in strategic processes during executive control. This region of the brain shows increased activity during errors, as well as during correct responses in which the task elicits response competition (Carter et al., 1998). In a recent fMRI study during the Érickson response conflict task, when subjects’ performance showed evidence of strategic processes being engaged to reduce the amount of response conflict, ACC activity was low. However, during trials in which their performance suggested that control was relaxed and conflict high (Botvinick et al., 1999), ACC activity was high. These data suggest that rather than directly implementing top-down control, the ACC serves an evaluative function, detecting conditions in the brain that are likely to be associated with poor performance (such as response conflict) and indicating the need for control to be more fully engaged.

Methods

In the present study we used event-related fMRI and a task-switching version of the Stroop task to test the hypothesis that the DLPFC and ACC serve complementary functions during executive control, with DLPFC activity being associated with representing and maintaining an attentional set to support task appropriate behavior, while the ACC detects response conflict which may signal the need for strategic processes to be more strongly engaged. Data were acquired on a 1.5-T GE scanner using a two-shot spiral pulse sequence. Each trial began with a cue informing subjects to either color name or word read during that trial. After a 12.5-s delay, during which five 2.5-s fMRI scans were acquired, a colored word was presented and subjects responded. A 12.5-s interstimulus interval ensued during which an additional five 2.5-s fMRI scans were acquired, followed by presentation of the cue for the next trial. Stroop stimuli could be either color congruent (e.g., RED printed in red) or incongruent (e.g., RED printed in blue). Word reading, color naming, and the presentation of congruent and incongruent stimuli were fully randomized across the experiment. Brain regions involved in top-down support were predicted to show activity during the preparatory period between the cue and the Stroop stimulus, which would be greater on color naming than on word reading trials. Brain regions involved in performance monitoring were predicted to show only response-related activity which would be greatest during incongruent color-naming trials, on which response conflict was highest.

Results

Error rates were very low and data were analyzed for correct trials only. Left DLPFC showed cue-related activity which was greater for color naming than word reading. BOLD activity in this region increased within 5 s after the onset of the cue and was significantly higher for color naming than for word reading trials. No other region of the brain showed this pattern. In addition, across subjects greater activation in left DLPFC correlated with smaller Stroop effects ($r = -.63$), supporting the interpretation that activity in this region is associated with strategic processes. In marked contrast to the DLPFC, ACC showed no evidence of cue-related activity, showing instead the same pattern of response-related activity previously reported (Carter et al., 1998; Botvinick et al., 1999), which was greater for incongruent color-naming trials. ACC activity correlated positively with the RT Stroop effect ($r = .41$).
FIG. 1. DLPFC and ACC activation during the task-switching Stroop task. Left DLPFC was cue related and greater for word reading than color-naming trials. ACC activation was response related and greater during incongruent color-naming trials.

consistent with the interpretation that activity in this region reflected the degree of response conflict elicited by the task, rather than any operation related to top-down control (Fig. 1).

Discussion

These data suggest that the DLPFC and the ACC have dissociable roles during task performance requiring executive control. The pattern of activity in the DLPFC and the association between activation in this area and better task performance are consistent with a role for this region in providing top-down support for task-appropriate behavior. This is consistent with neuropsychological, functional imaging and single-cell recording data related to the function of this region of the brain. In contrast, activity in the ACC suggests a distinctly different, complementary function for this region of the brain during executive control. As we have observed in previous studies, during correct responses activity in the ACC tracked the degree of response conflict elicited by the task. This pattern of activity together with the correlation between the ACC and worse performance is consistent with the hypothesis that this region of the brain serves an evaluative function, detecting response conflict and signaling the need for control to be engaged.

Further studies are needed to confirm the dissociation observed in the present study, and the interpretation of the neuroimaging data reported here would be informed by the results of single-cell recording studies in DLPFC and ACC during tasks such as the Stroop. Such studies have the potential to reveal the pattern of neuronal firing associated with the unique contributions of these two regions to executive control. Previous electrophysiological studies have suggested that ACC activity is correlated with on-line adjustments in strategy (Ghering et al., 1993). Future studies should have as their goal a detailed analysis of the mechanisms by which performance monitoring by the ACC is coupled to modulations of activity in areas such as DLPFC, where strategic adjustments appear to be implemented in the human brain.

REFERENCES


12. Prefrontal Cortical Activation during Word-Associative, Face-Associative, and Word–Face-Associative Encoding

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We report a fMRI study of associative encoding. Subjects studied blocks of word pairs, face pairs, and word–face pairs under two encoding instructions, which either involved judgments about the individual items comprising the pairs or required subjects to associate the items. Comparisons between these two encoding conditions revealed the following. First, consistent with HERA, for both face pairs and word pairs there was a large overlapping region of activation which was left lateralized, with little evidence of material specificity. Second, this activation involved principally Brodmann areas 8 and 9, a region more dorsal than those previously reported. Third, the activation pattern for encoding associations between different kinds of items, word–face pairs, was different from the first pattern and involved bilateral anterior portions of area 47.

Functional imaging studies of memory have consistently revealed significant activations in prefrontal cortical (PFC) regions. The recruitment of these regions during both encoding and retrieval and the fact that such activations often cooccur with activations in the medial temporal lobe (MTL) suggest that a network of interconnected brain regions is involved in human memory (Mayes & Montaldi, 1999). Tulving, Kapur, Craik, Moscovitch, and Houle (1994) noted certain regularities about these memory-related activations. In their hemispheric encoding retrieval asymmetry (HERA) model, they claimed that memory encoding tasks resulted in predominantly left-lateralized activation, whereas retrieval operations produced right-lateralized activations. Few of these earlier studies employed nonverbal materials, so there is currently some debate about whether these patterns conflict with the classic material-specific hemispheric-specialization view (see McDermott, Buckner, Petersen, Kelley, & Sanders, 1999). In relation to encoding, there is also some debate about the critical PFC regions activated (Fletcher, Shallice, & Dolan, 1998): There is consensus that the encoding of single words, for example, activates a region in the vicinity of the left inferior frontal gyrus and some, but not all, studies using single unfamiliar faces have reported activations in the homologous right-lateralized region (McDermott et al., 1999). However, there is also recent evidence suggesting that the primary site of activation may shift as a function of the specific (word) encoding demands (Fletcher et al., 1998). To explore these issues further, subjects underwent fMRI scans while viewing different types of stimulus pairings (word–word, face–face, word–face) which were orthogonally crossed with two types of encoding. Subjects
were instructed either to make separate judgments about the individual members of stimulus pairs or to associate them in some meaningful way.

Participants

Ten right-handed student volunteers (3 male), all with normal uncorrected vision, participated in the experiment for which they were paid a small honorarium.

Behavioral Tasks and fMRI Methods

Before fMRI scanning, all were trained on the behavioral tasks. The stimuli comprised pairs of unrelated words, pairs of unfamiliar faces (one male and one female), and pairs comprising a word and a face. The pairs were separated either by a plus sign (+) or by a vertical line (|). When the plus sign was present, subjects were instructed to form a novel association between the two stimuli (associative encoding). In the case of words this entailed linking the words in some elaborative way and subjects were encouraged to use imagery. In the case of faces, associative encoding involved making a decision about the compatibility of the male–female pairings. For the word–face pairings, subjects were encouraged to try to make some link between the person depicted and the accompanying word. When the vertical line was present, subjects were taught to assess the pleasantness of the stimuli separately (single encoding). The final condition was the low-level baseline, in which subjects saw two rectangular black and white noise images and were asked to decide whether the two were identical or not. The stimuli comprised 75 unrelated words, matched for frequency, and 75 black and white photographs of faces. Stimuli were presented to the subjects in the scanner using a PC and an Epson LMP7300 liquid crystal display projector. The images were back projected onto a screen, which was visible from the scanner bore via a combination of mirrors. Following the scanning session, subjects’ memory was tested.

MR imaging was performed using a 1.5-T LX/Nvi Neuro-Optimized MR imaging system (General Electric, Milwaukee, WI), which has 40 mT/m gradients. Functional images were 22 contiguous T2* weighted gradient-echo echoplanar images (EPI) with echo time (TE) of 40 ms, repetition time (TR) of 3 s, flip angle of 90°, matrix of $64 \times 64$, a 24-cm field of view, and a slice thickness of 5 mm. The images were oriented parallel to the line between the anterior and posterior commissures (AC–PC line) and covered the entire cerebrum.

Each functional run consisting of 160 EPI volume acquisitions took 8 min and was divided into 15 epochs each 33 s in length. Three conditions (5 epochs each) were presented in each functional run and were arranged in a random order. In the first 3 s of each epoch a title appeared to inform the subject what the next epoch would be. Five pairs of stimuli were presented for 6 s each per epoch. The runs were: (1) Words (associative encoding, single encoding, and low-level baseline); (2) Faces (as with words); (3) Word–face (as with words); and (4) Cross-condition (word–word, face–face, and word–face, associatively encoded in each case). The order of the runs was counterbalanced. Data were motion corrected and spatially normalized to a template brain before group analysis. Functional data were analyzed using SPM software (<http://www.fil.ion.ucl.ac.uk/>).

Results and Discussion

For the present purposes, we focus on the specific comparisons between the associative and single encoding conditions for each stimulus type. PFC activation sites, cluster sizes, and Z scores are shown in Table 1.
TABLE 1
Prefrontal Cortex Regions Associated with Significant Activation in the Associative vs Single Encoding Comparisons

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Prefrontal region</th>
<th>Cluster size</th>
<th>Z score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Words</td>
<td>L superior gyrus, BA 8,9</td>
<td>109</td>
<td>7.16</td>
</tr>
<tr>
<td></td>
<td>L middle gyrus, BA 46</td>
<td>6</td>
<td>5.39</td>
</tr>
<tr>
<td></td>
<td>L middle sulcus, BA 45</td>
<td>10</td>
<td>5.32</td>
</tr>
<tr>
<td></td>
<td>L middle gyrus, BA 44</td>
<td>6</td>
<td>5.29</td>
</tr>
<tr>
<td>Faces</td>
<td>L superior sulcus, BA 8</td>
<td>36</td>
<td>6.91</td>
</tr>
<tr>
<td></td>
<td>L middle gyrus, BA 9</td>
<td>17</td>
<td>6.86</td>
</tr>
<tr>
<td></td>
<td>R middle sulcus, BA 44</td>
<td>6</td>
<td>5.81</td>
</tr>
<tr>
<td></td>
<td>L middle gyrus, BA 46</td>
<td>8</td>
<td>5.54</td>
</tr>
<tr>
<td></td>
<td>L middle sulcus, BA 44</td>
<td>4</td>
<td>5.00</td>
</tr>
<tr>
<td>Word–face</td>
<td>L anterior inferior sulcus, BA 47</td>
<td>12</td>
<td>5.37</td>
</tr>
<tr>
<td></td>
<td>R anterior inferior sulcus, BA 47</td>
<td>8</td>
<td>5.31</td>
</tr>
</tbody>
</table>

Three important findings emerge from these comparisons. First, the pattern of activations overlapped considerably for word pairs and face pairs. In both cases this was predominantly left lateralized, the only evidence of material specificity being a small right-lateralized region in area 44, activated for the face pairs. Thus, for the higher-level associative encoding tasks employed here, the observed activations are consistent with HERA.

Second, the principal region activated included areas of the superior frontal gyrus/sulcus encroaching Brodmann areas 8 and 9. There were also smaller sites of activation around the middle frontal gyrus/sulcus, corresponding to areas 44 and 46. It is unlikely that the portion of this activated region lying in area 8 was due to eye movements, because alternating conjugate eye movements would produce bilateral activation. Results from several studies (see Fletcher et al., 1998) have shown that the encoding of single words, irrespective of encoding task demands, is associated with activation of the left inferior frontal gyrus, and more recently Fletcher et al. (1998) have found that encoding tasks requiring the organization of single words according to their semantic attributes involves a more dorsal region of left PFC. The present findings suggest an extension to this ventral–dorsal pattern, because the more complex associative task of integrating semantically unrelated words activates yet more dorsal regions. Face-pair-associative encoding may activate the same regions as word-pair-associative encoding because judgments about the compatibility of male–female pairings are meaningful, in the sense that they are interpretable and communicable, but are also most likely based on complex (abstract) heuristic processes.

The third important finding is that the activation patterns are different depending on whether the associations to be encoded involve material from the same or different modalities. Thus, associative encoding of word–face pairs resulted in bilateral activation of small regions of area 47 anteriorly. It is possible that the left-lateralized activations described above, and not evident in the word–face comparison, may relate to the difficulty of meaningfully relating words with faces. However, the available behavioral data we have suggests that memory was worst, not for the word–face pairs, but for the face pairs.

In summary, our study shows that the encoding of associations activates additional, more dorsal regions of left PFC than the encoding of single items, a pattern which holds for both words and faces. In contrast, the encoding of associations between different kinds of item results in very little additional activation, in this case located bilaterally in area 47.
13. Working Memory for Faces: An fMRI Study of Prefrontal and Extrastriate Visual Cortex

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During BOLD fMRI scanning, subjects performed an N-back task for gray-scale faces. The N of the task was varied parametrically from 0-back to 1-back to 2-back. Voxels in the prefrontal cortex (PFC) and fusiform face area (FFA) were tested for linear increases with N of the N-back. This study replicated a previous finding that PFC activation increases directly with task load. The novel finding of the study was that FFA activation also increases directly with task load over the entire region of interest. Since the perceptual demands were equal across task conditions, these findings suggest that both the PFC and the FFA play a significant role in the working memory component of the task.

Introduction

Previous fMRI studies of human visual working memory tasks have suggested that extrastriate visual areas have a predominant role in perceptual processing (Kanwisher, 1997) while prefrontal cortex (PFC) has a predominant role in working memory (Courtney, 1997). In contrast, neurophysiology studies in monkeys have shown evidence of a role for extrastriate visual areas in the working memory component of the tasks performed (Chelazzi, 1998). In this study we tested whether activity in both the PFC and FFA changed with increasing demands of an N-back task for faces. The N-back task allowed us to control the perceptual demands of the task since the stimulus presentation was identical across conditions, with task instructions as the only difference.

During BOLD fMRI scanning, subjects were required to perform a blocked N-back task for gray-scale faces. At the beginning of each 30-s block, subjects were shown an instruction to perform one of three tasks: 0-back, 1-back, or 2-back. Following the instruction, a single face stimulus was presented every 2 s, with each stimulus remaining on the screen for 1 s. In the 0-back task subjects were instructed to respond to a target face. A general linear model for correlated observations was used to test voxels for linear increases with N of the N-back.

This study replicated the result that the PFC shows areas of activation that increase...
directly with the demands of the task. The novel finding is that subjects demonstrated FFA activation which increased directly with the demands of the task. Since the perceptual demands are equal across the three task conditions, these findings suggest that both the PFC and the FFA play a significant role in the working memory component of the task.

Methods

Subjects. Nine right-handed subjects (age range 21–27 years) were recruited from the University of Pennsylvania Medical School. All participants were screened for medical, neurological, and psychiatric illnesses and also for use of prescription medication. Subjects were trained to a predetermined criterion on the task the day prior to the scan.

N-back task for faces. Subjects were presented with an instruction (0-back, 1-back, or 2-back) for 4 s, followed by a sequence of 13 gray-scale faces. Faces appeared for 1 s at a time, followed by 1 s of fixation. In the 0-back condition, subjects responded with a button press to a predetermined target face. In the 1-back condition, subjects responded when a face matched the previous stimulus. In the 2-back condition, subjects responded when a face matched the one presented two stimuli beforehand. The experiment was structured in 30-s condition blocks presented in a pseudo-randomized order.

Image acquisition. Imaging was carried out on a 1.5-T Signa scanner (GE Medical Systems) equipped with a fast gradient echoplanar imaging system. A standard radiofrequency head coil was used with foam padding to restrict head motion. High-resolution sagittal and axial T1-weighted images were obtained in every subject. A gradient echo, echoplanar sequence (TR = 2000 ms, TE = 50 ms) was used to acquire data sensitive to BOLD signal. Resolution was 3.75 mm² in plane and 5 mm between planes (21 axial slices). Twenty seconds of gradient and RF pulses preceded data acquisition to allow steady-state tissue magnetization.

Data preparation. Data preparation proceeded as follows: image reconstruction; sinc interpolation in time (to correct for fMRI slice acquisition sequence); motion correction (six-parameter, rigid-body, least-squares realignment); and slicewise motion compensation (to remove spatially coherent signal changes via application of a partial correlation method to each slice in time). Because fMRI data are temporally autocorrelated under the null hypothesis, data analysis was conducted within the framework of the modified general linear model for serially correlated error terms.

Identification of the fusiform face area. Subjects passively viewed 20-s blocks of gray-scale faces and objects over a single scan. The FFA was individually defined as all voxels in the anatomically defined fusiform gyrus showing statistically significant activation in a contrast of faces vs objects.

Analysis for linear trends. The three task conditions appeared in pseudo-randomized 30-s blocks. Using the modified general linear model, a mean parameter estimate was obtained for each block. Linear regression of the parameter estimates onto a numerical index of condition (0, 1, or 2) gave a slope of the linear trend and a statistical significance of that trend.

Results

Linear increases with N of the N-back task appear in a Subset of PFC voxels. The PFC region of interest was defined anatomically for each individual subject. In eight of nine subjects, there were voxels within the PFC that demonstrated a statistically significant linear increase with N of the N-back. The locations of these
voxels were not consistent across subjects, but were generally more dorsal than ventral.

*Linear increases with $N$ of the N-back task appear in a subset of FFA voxels.* The FFA region of interest was functionally defined, as previously described. In seven of nine subjects, there were voxels within the FFA that demonstrated a statistically significant linear increase with $N$ of the $N$-back. The location of these voxels generally overlapped those voxels which showed the highest $t$ values in identification of FFA.

*Linear increases with $N$ of the N-back task appear over the entire FFA.* Mean parameter estimates of each condition block were obtained across all voxels in the FFA for each subject (32 blocks per condition × 3 conditions). Linear regression of the parameter estimates onto an index of condition (0, 1, or 2) gives a line with slope $\beta$ and an associated $p$ value. $\beta$ is a measure of how activation changes with condition; the $p$ value assesses the significance of this change. All nine subjects showed increases in activation with the index of condition, and seven of nine subjects showed increases at $p < .05$.

**Discussion**

This study replicated the result that the PFC shows areas of activation that increase directly with the demands of the task (Braver, 1997). The novel finding was that subjects demonstrated FFA activation which increased directly with the demands of the task. Since the perceptual demands were equal across the three task conditions, these findings suggest that both the PFC and the FFA play a significant role in the working memory component of the task.

Although this study found linear changes with $N$ of the $N$-back task in both the PFC and FFA, it remains difficult to assess if these changes are truly linear. Since subjects were not able to behaviorally perform a 3-back task, it was impossible to add a fourth level of difficulty to the experiment. While the regressions come out statistically significant, the essential task of regressing a line onto only three independent variables makes us skeptical of the linearity of this relationship. However, we are confident in saying that the level of activity increases as the difficulty increased from 0-back to 1-back to 2-back.

While the findings of this study were significant, a number of issues are left to be investigated by future experiments. It was unclear which aspect of increasing $N$ of the $N$-back resulted in the linear increases of activation. Since the location of linear FFA voxels generally coincided with those showing the highest $t$ values in identifying the FFA, the increases in the FFA were unlikely to be the result of a general attentional modulation of extrastriate visual cortex. A more specialized attentional modulation cannot be ruled out (Wojciulik, 1998). If the increases were related more to the working memory components of the task, it is unclear whether the increases were attributable to the increased memory load or to the increased manipulation demands that occurred at different task levels. These possibilities will be addressed in a subsequent experiment using a working memory paradigm which removes these confounds.

**REFERENCES**


14. A Midfrontal Scalp ERP Old/New Effect for Unfamiliar Stimuli: Possible Functional and Anatomical Correlates

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Recent studies suggested that a mid-fronto-temporal ERP memory effect reflects the inhibition of proactive interference subserved by the ventrofrontal cortex. In this study, ERPs were recorded in a protocol manipulating proactive interference through the number of items intervening between the first and the second presentation of a stimulus. The results obtained in 24 subjects showed a mid-frontal ERP effect which changes across lags is compatible with an interpretation in terms of proactive interference inhibition. The results are also discussed with respect to recent studies of intracranial recordings from the ventrofrontal structures that provided very similar findings. © 2001 Academic Press

Introduction

One of the most consistent finding in ERP and memory is that ERPs evoked by previously presented (old) stimuli are more positive going than ERPs evoked by stimuli on their first presentation, (new) items (Rugg & Doyle, 1994). This ‘ERP old/new effect’ is composed of several effects different in their timing (encompassing the N4 and/or the P6 components), their task correlates, and their scalp topography, each one reflecting distinct neurocognitive processes necessary for memory learning and retrieval.

Of particular interest is a recently described midfrontotemporal effect elicited within 300–700 ms poststimulus (Curran, 1999; Guillem et al., 1999a). This effect appears to be elicited only in situations requiring the explicit learning of unfamiliar information (i.e., pseudo-words or unfamiliar faces). The characteristic common to these stimuli is that they have no stable preexisting representation in memory. During learning, this makes them very sensitive to proactive interference from the potentially confounding information associated with previously memorized stimuli. This is not the case for familiar stimuli, which have, by definition, a more stable, or consolidated, representation in memory. Accordingly, the greater amplitude of the midfrontal N4 observed for unfamiliar information has been suggested to reflect the greater amount of selective inhibition necessary to prevent incoming information from proactive interference (Guillem et al., 1999a). The midfrontotemporal distribution of the effect is compatible with a ventrofrontal origin (i.e., the inferior and orbital–frontal cortices), a brain region known to play a major role in the maintenance of novel information over interference (Fuster, 1980). Nevertheless, this interpretation remained to be confirmed in a situation specifically designed to assess the effect of proactive interference.
This paper presents results that may further support this interpretation. In this study, ERPs elicited by unfamiliar faces were recorded in a protocol in which proactive interference are manipulated through the interitem lag, i.e., the number of items intervening between the first and the second presentation of a stimulus.

**Method**

Twenty-four right handed volunteers (14 males, 10 females, mean age 26.3 years) participated in this experiment.

The stimuli consisted of 438 color photographs of unfamiliar faces taken from the MED bank (see Guillem et al., 1999a) presented on a computer screen for a 500-ms duration with an ISI of 6 to 8 s. Three blocks were constructed in which the stimuli were placed in a pseudo-random order in a continuous task sequence. In each block, 73 faces were presented a first time (New) and reappeared subsequently once in the sequence: 13 reappeared after a 2 intervening items (Old-2), 20 after a 6 intervening items (Old-6), and 40 after a 20 intervening items (Old-20). The subjects were required to indicate for each item whether it was an old or a new one by pressing the right or left arrow keys on a computer keyboard.

EEG was recorded from 13 electrodes placed according to the 10–20 system. Vertical and horizontal EOG were monitored via electrodes placed below and on the outer canthus of the left eye, respectively, and Fpz served as the ground. Electrodes were referenced to the right earlobe. Impedance of all electrodes was maintained below 5 kΩ. Continuous EEG was recorded (bandpass of 0.01–30 Hz), digitized online (250Hz) and averaged offline after artifact rejection. For the direct and indirect tests, ERPs were computed separately for new and repeated items with a 200-ms prestimulus baseline and a 1000-ms poststimulus interval.

ERPs corresponding to correctly classified new and old items were computed separately. ERP analysis began by wave identification by visual inspection of the grand-average waveforms from the midline sites (Fz, Cz, Pz). For each condition and for each electrode site, amplitudes were subsequently measured with respect to the 200-ms prestimulus baseline. The data were normalized according to the McCarthy and Wood’s procedure to eliminate overall amplitude differences in scalp distribution across conditions. Main effects were assessed using ANOVAs (Greenhouse–Geisser correction) with the ‘condition’ (4 levels) and electrode ‘site’ (13 levels) as within-subject variables. When appropriate (i.e., significant condition × site interaction) partial ANOVAs were used to assess the ERP old/new effect for each lag (New/Old-2, New/Old-6, New/Old-20) and at each site.

**Results**

ERPs were characterized by a series of four waves: N2 (201–315 ms), P3 (315–410 ms), N4 (410–526 ms), and a P6 (526–714 ms). For all waves there were a significant effect of site, the effect of condition was present only for the N4 and P6, and there was a significant interaction between site and conditions only for the N4.

Subsequent examination of the scalp topography and partial analyses on the N4 data (Fig. 1) revealed an ERP old/new effect prominent over frontocentral (Fz, Cz) and midfrontal sites (Fp1, Fp2). This effect, which was present at each lag condition, tended to increase with greater lags (dotted lines in Fig. 1). The examination of the ERP curves showed that this was due to a tendency for the N4 amplitude to decrease with increasing lags, particularly between Old-6 and Old-20, at right midfrontal (Fp1, Fp2) and lateral frontal (F8) sites. The maximum effect observed at Old-2 condition
FIG. 1. Normalized ERP (N4) amplitudes and significance ($p$ values) of the ERP old/new effect for each condition and at each site. Dotted lines showed the progressive increase of the midfrontal effect.
suggests a superimposed short-term effect with a frontocentral (Fz, Cz) and parietal (P3) distribution. Other marginal effects present at posterior sites (T5, T6) will not be discussed here.

Discussion

With the unfamiliar stimuli used, an ERP old/new effect with a midfrontal topography was present at all lags during the N4 time window. This component showed a tendency to decrease progressively with the number of intervening items. This tendency is compatible with the view that this midfrontal ERP (N4) old/new effect is related to the inhibition of proactive interference. Indeed, proactive interference refers to the interference produced by previously memorized information on the processing of new ones. The effect of such interference is temporary and decreases as the representation of information in memory stabilizes, or consolidates, in long-term memory. On the contrary, the newer the information (i.e., first presentation or short lags) the more the inhibition should be required to prevent proactive interference.

Given the role of the ventrofrontal cortex in the inhibition of proactive interference, it is of note that recent studies obtained by direct intracranial recordings from frontal structures showed results very similar to those reported here (Guillem et al., 1999b). In the ventrofrontal structures, an ERP old/new effect is present at both short and long lags, with the N4 showing a tendency to decrease with increasing lags. As a matter of fact, the midfrontal (Fp1, Fp2) and lateral frontal (F8) topography of the present effect suggests a ventrofrontal origin. By contrast, at electrodes located within the dorsolateral cortex the effect is present only at short lags. This could be reflected, in the present study, by the short-term (Old-2) effect observed at frontocentral (Fz, Cz) sites, which overlaps (or is superimposed to) the previous effect. On the other hand, these results suggest that carefully selecting appropriate variables (i.e., stimuli and task variables) on the basis of knowledge accumulated in cognitive neuropsychology is relevant. It could allow building protocols that provide, on the scalp, ERP indices specifically related to the functioning of particular brain regions without necessarily having recourse to source analysis.

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15. Functional Imaging Dissociations within Right Prefrontal Cortex during Episodic Memory Retrieval

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Several different interpretations have been advanced for the consistent activation of right prefrontal cortex during neuroimaging studies of episodic memory retrieval. We propose that the reasons for these conflicting hypotheses include (1) lack of appropriate psychological models of the retrieval process and (2) existence of at least three functionally specialized prefrontal subregions: dorsolateral (BA 9/46), ventrolateral (BA 45/47), and anterior (BA 10) cortex. In recent imaging studies from our laboratory, we have reported dissociations between ventrolateral and dorsolateral regions and between dorsolateral and anterior regions. Using a process model developed to explain confabulations following frontal lesions, we interpret the ventrolateral versus dorsolateral dissociation in terms of cue specification versus retrieval monitoring. Interpretation of anterior activations, however, which appear task sensitive, requires some extension of this model.

The right prefrontal cortex has been consistently activated in neuroimaging studies of retrieval from episodic memory. Interpretations of these activations include, among others, adoption of a retrieval mode, expenditure of retrieval effort, and engagement of postretrieval processing. We propose that at least two reasons for these conflicting hypotheses are (1) lack of adequate psychological models of the retrieval process, within which these hypotheses can be formally defined, and (2) existence of multiple subregions within prefrontal cortex that subserve distinct functions during episodic retrieval. Below we discuss a specific model of retrieval and how it might map onto the three anatomically distinct regions of dorsolateral (DLPFC, BA 9/46), ventrolateral (VLPFC, BA 45/47), and anterior (APFC, BA 10) right prefrontal cortex, based on a review of recent imaging experiments from our laboratory.

To account for the protocols recorded while healthy volunteers recalled autobiographical memories, Burgess and Shallice (1986) proposed a model of retrieval that included two key components: descriptive processes, including specification of retrieval cues, and editing processes, including monitoring the products of retrieval cueing. When asked ‘‘what was your most recent trip abroad?’’ for example, one might specify cues such as ‘‘beach’’ and ‘‘airport’’ in order to retrieve memories of trips abroad. Monitoring of the retrieved information is then necessary to select which corresponds to the most recent trip. The different types of confabulations following frontal lesions can be attributed to damage to one or more of these processes (Burgess & Shallice, 1986).

Fletcher et al. (1998) reported a double dissociation between right VLPFC and DLPFC activation when comparing cued recall with free recall. Healthy participants studied category–exemplar word pairs and were scanned with PET during recall that was either prompted with the categories (cued recall) or prompted with the word ‘‘next?’’ (free recall). VLPFC was more active for cued than free recall, whereas DLPFC was more active for free than cued recall. This pattern can be explained if VLPFC is involved in specifying retrieval cues (with the assumption that cued recall entailed greater variation of cues) and DLPFC is involved in monitoring retrieval (with the assumption that free recall required greater monitoring in order to prevent, for example, repetition of responses).
Henson et al. (1999a) reported a single dissociation between right VLPFC and DLPFC during two word recognition conditions that involved identical stimuli, differing only in task instructions. Words were studied in one of two spatiotemporal contexts and then tested in either an Inclusion condition, which required simple yes/no recognition decisions, or an Exclusion condition, in which recognition decisions were contingent upon the study context (source). When the Inclusion condition was compared against a control condition, both VLPFC and DLPFC were activated, consistent with both cueing and monitoring of episodic retrieval. Direct comparison of the Exclusion versus Inclusion condition however revealed activation of DLPFC alone, consistent with greater monitoring demands when source information must be used to guide responses. The lack of differential VLPFC activation is consistent with the view that the dominant retrieval cue during recognition is a ‘copy cue’ of the target itself, which was identical across Inclusion and Exclusion conditions. Moreover, the degree to which DLPFC activity predicted VLPFC activity increased from the Inclusion to Exclusion conditions, consistent with a tighter functional coupling between the two regions when retrieved information must be monitored closely.

Henson et al. (1999b) reported activation of right DLPFC under conditions in which source retrieval and monitoring could be dissociated. Using event-related fMRI during word recognition, participants indicated with a ‘Remember’ judgment those words that elicited recollection of the previous study episode, with a ‘Know’ judgment those words that elicited a feeling of familiarity in the absence of recollection, and with a ‘New’ judgment those words not recognized. The only right prefrontal region differentially active for Remember and Know judgments was DLPFC, which was more active for Know judgments (source retrieval, which is more likely associated with the opposite comparison of Remember versus Know judgments, activated only left prefrontal regions). The authors proposed that feelings of familiarity, in the absence of confirmatory recollection, require greater monitoring before a word is endorsed as old (i.e., given a Know judgment). This is consistent with the longer reaction times that accompanied Know judgments. Right VLPFC was not differentially activated for Remember versus New judgments, consistent with copy cues being used to probe memory for both old and new words (even if only successful in the former case). Right VLPFC was, however, more active for Know than New judgments, which may reflect specification of alternative retrieval cues when recollection fails.

Henson et al. (submitted) reported a double dissociation between right DLPFC and APFC. In this event-related fMRI study, participants made one of four judgments during word recognition: whether each word was ‘Old’ or ‘New’ and whether each old-new judgment was made with ‘High’ or ‘Low’ confidence. Using a signal-detection model of recognition, in which memory strengths (or familiarity levels) are viewed as a continuum, the authors predicted greater DLPFC activity associated with Low than High confidence judgments, regardless of whether words were old or new. This prediction was based on the assumption that monitoring demands are maximal when memory strengths are close to the old–new response criterion. This prediction was confirmed and reinforces the conclusions of Henson et al. (1999b) that right DLPFC is more active when memory judgments are uncertain (and reaction times are longer). Right APFC however was more active for correct Old versus correct New judgments. This finding suggests that right APFC is engaged in situations in which episodic retrieval is successful (i.e., memory strengths are high and/or accompanied by recollection).

Rugg et al. (1998) however reported activation of right APFC that was differentially sensitive to retrieval success as a function of retrieval task. Participants were scanned with PET during either word-stem cued recall or word recognition and under two conditions: one in which none of the stems or words during the scanning window
corresponded to studied words (Zero-density condition) and another in which 80% of test stimuli corresponded to studied words (High-density condition). In agreement with previous studies and Henson et al. (submitted), right APFC was more active in the High-density than Zero-density condition during recognition, supporting the hypothesis that activation of this region reflects retrieval success. However, right APFC was more active under the Zero-density than High-density condition during cued recall, producing a double dissociation between target density and task. This finding implies that right APFC activation is not restricted to successful retrieval of episodic information. The authors suggested instead that activation of APFC reflects processes operating on both the products of episodic and semantic retrieval. In the case of word-stem cued recall, multiple completions for each stem can be generated by repeatedly probing semantic memory. In the High-density cued recall condition, one of these completions may be recognized as old (corresponding to a study word). In the Zero-density condition, however, many more completions will be generated, on average, because none of the completions correspond to study words. This proposal is similar to the monitoring processes attributed to right DLPFC, but is contingent on successful retrieval of episodic or semantic information.

The above review of functional dissociations between right VLPFC and DLPFC during episodic retrieval is consistent for a role of VLPFC in specifying retrieval cues and for DLPFC in monitoring the products of retrieval cueing. This dissociation bears some resemblance to the maintenance versus manipulation distinction for VLPFC and DLPFC that has been proposed from imaging studies of working memory (which is to be expected, given that complex retrieval operations are likely to involve working memory). The functional dissociation of DLPFC and APFC is less clear cut and does not map so easily onto the Burgess and Shallice (1986) model. One clear goal for future studies is to present detailed task analyses of different retrieval tests, which may require extension of the Burgess and Shallice model (e.g., to distinguish different types of monitoring for different tasks and different types of information). Another future goal concerns the role of left prefrontal cortex during episodic retrieval. Left DLPFC was activated in, for example, the Exclusion versus Inclusion comparison of Henson et al. (1999a) and the Low versus High confidence comparison of Henson et al. (submitted) and may subserve monitoring processes similar to those proposed for right DLPFC. Left APFC was activated in the Remember versus New comparison of Henson et al. (1999b) and the Old versus New comparison of Henson et al. (submitted) and is likely to reflect processes associated with source retrieval. This possible lateralization of prefrontal function during episodic retrieval is still a matter of debate and may benefit from studies of memory deficits following lateralized frontal lesions.

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16. Working Memory Load Is Reflected by a Change in the Alpha and Theta ERP Components in a Verbal “Two-Back” Paradigm

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Introduction

During the past years, several studies have used the “two-back” paradigm (comparing the presented stimulus with the one before the last) to investigate working memory (WM). In this ERP study we focus on the significance of the number of repetitions in critical and noncritical positions within the presentation sequence. Increasing the number of repetitions in noncritical positions makes it necessary to distinguish between different degrees of recency of the presented targets and to decide if the actual target fits in with a specific position within the sequence. To analyze the influence of noncritical conditions we compare three conditions: (1) a recognition control task, (2) a task with target words repeated only in critical positions, and (3) a task with words repeated in critical and in noncritical positions.

Method

Twelve subjects (students of psychology) participated in the study. They were seated facing a computer screen and watched a sequence of words (composed of four or five letters). They were instructed to press a “Yes” or “No” key at each trial, depending on the task and the presented item. We recorded behavioral data (response time and omissions) and ERPs from eight electrode sites placed in a 10–20 system montage (Fz, Cz, Pz, and Oz and F3, F4, T5, and T6). Analysis included ERP components (N2, P3) derived from artifact-free EEG epochs and the frequency bands of theta (4–7 Hz), and alpha (8–12 Hz). ERP frequency analysis was performed by means of fast Fourier transform (FFT). Integrals over intervals of amplitude frequency characteristics were used to analyze the influence of the experimental conditions on the frequency bands.

We analyzed response times, error rate, and ERP results by MANOVA for repeated measurement. Analysis of the ERP results focused on a midline model (Fz and Cz for frontal sites and Pz and Oz for posterior sites) and a lateral model (F3 and F4 for frontal sites, T5 and T6 for posterior sites; F3 and T5 for left hemisphere, and F4 and T6 for right hemisphere electrodes).

Results

All data were evaluated by a repeated measures analysis of variance and a Greenhouse–Geisser correction for multiple testing and small sample size. The behavioral
FIG. 1. Increase with the theta band at frontal electrodes.

data showed a linear increase of response time and omissions from task 1 to 3, arguing for a gradual increase of WM load from task 2 to task 3. There were no significant differences in the P3 latencies, but the P3 amplitudes decreased from task 1 to task 3. For the lateral model (F3, F4, T5, T6), but not for the midline model (Fz, Cz, Pz, Oz), the alpha component increased significantly related to task \[ F(2, 11) = 4.049, \ p = .045 \]. The theta component showed a significant increase due to task in the lateral model \[ F(2, 11) = 5.523, \ p = .020 \] and an interaction between task and frontal versus postcentral electrode site in the midline model \[ F(2, 11) = 4.654, \ p = .024 \] (see Fig. 1).

Discussion

As a conclusion we would like to argue (1) that the frequency of the presentation of a single stimulus in critical and noncritical positions is an important factor of WM load to be controlled for in a two-back paradigm and (2) that the increase in WM load is reflected by a general increase of alpha at the lateral sites and by a theta increase at midline frontal and central sites not visible at midline parietal and occipital sites.

Gevins et al. (1997, 1998), using a three-back paradigm, found for a continuous EEG mapping a decrease of alpha and an enhancement of theta at Fz, whereas both components did not change in relation to WM load at posterior sites. Our results extend the findings of Gevins for a stimulus-locked ERP frequency analysis. In our two-back verbal WM paradigm the theta component significantly increased for Fz and Cz, but was reduced at the parietal and occipital sites. There was no task-related change for F3 and F4, though studies using functional brain imaging (Braver et al., 1997; Callicott et al., 1999) have shown a significant involvement of the dorsolateral frontal lobe in WM. The enhancement of theta at the midline frontal electrodes in our and the Gevins et al. study might be due to the activation of the anterior cingulate as a structure responsible for response selection, response inhibition, and selective attention. Another possibility would be that the anterior cingulate is involved in recency judgment (Eyler-Zorrilla et al., 1996) and became activated in the condition with high WM load, where critical and noncritical positions of words were to be discriminated.
17. Biochemical Markers of Mood: A Proton MR Spectroscopy Study of Normal Brain

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Magnetic resonance spectroscopy and imaging (MRS, MRI) have become useful tools for in vivo chemical and structural analysis in disease and health. In mood disorders, researchers utilizing MRI have found significantly decreased volume, blood flow, and metabolism in the prefrontal cortex and basal ganglia. Metabolic abnormalities, such as elevated choline (Cho) in the basal ganglia, have also been shown in these disorders. However, the roles of neurometabolites such as Cho in normal mood functioning have not been well characterized. In the current study we wanted to explore the relationship between proton (1H-MRS) metabolic measures and mood in healthy young subjects. Complete spectroscopy and scores from the positive affect negative affect scale (PANAS) were obtained from 24 subjects. We found that levels of Cho in the left frontal lobe were inversely correlated with measures of Positive Affect ($F = 31.31, p < .0001; r^2 = .59$). The implications of this research finding to mood disorders are discussed. © 2001 Academic Press

Introduction

The extent to which frontal lobe integrity contributes to affect has been researched extensively utilizing structural and functional magnetic resonance imaging (MRI; fMRI), positron emission tomography (PET), and lesion studies. For example, researchers have found significantly decreased volume, blood flow, and metabolism in the prefrontal cortex and basal ganglia of unipolar, bipolar, and patients with late life minor depression (Soares & Mann 1997). Similarly, left anterior and right posterior stroke is well associated with depression, while right anterior and left posterior stroke patients are less likely to be depressed. However, the specific neurochemical correlates of these structural and functional abnormalities are poorly understood.

A rather recent technique to assess brain integrity has emerged from studies utilizing magnetic resonance spectroscopy (MRS), which provides a quantitative mea-
measurement of the neurochemical component of neural variation in vivo. Proton MRS (\(^1\)H-MRS) detects signals from metabolites including \(N\)-acetylaspartate (NAA), creatine (Cre), and choline-containing compounds (Cho). Reduced NAA has been associated with neuronal injury or death, impaired cognition, and poor functional outcome in numerous brain disorders. Further evidence also suggests that mitochondrial dysfunction may cause decreases in NAA. The Cre peak represents the sum of intracellular creatine and phosphocreatine associated with cellular energetics. The Cho peak reflects the sum of all \(^1\)H-MRS visible choline moieties and is commonly elevated in stroke and multiple sclerosis due to membrane breakdown, inflammation, and/or demyelination (Ross, 1994).

Researchers utilizing MRS have found metabolic abnormalities in the basal ganglia and frontal lobes of patients diagnosed with bipolar and major depressive disorders (Kato, 1998). Specifically, elevated Cho in the basal ganglia has been associated with bipolar disorder in numerous studies utilizing \(^1\)H-MRS. In the same studies, no spectroscopic differences were noted in occipital, temporal, and "cortical" structures. In major depression, similar elevations in the Cho resonance were evident in the basal ganglia, but not elsewhere in the brain. Frontal lobe phosphorous spectroscopy (\(^31\)P-MRS) has been measured in these patient groups and has revealed altered phosphomono- and diesters, phosphocreatine, and intracellular pH.

While the clinical correlates of altered neurometabolism have been well described in disease, the role of these chemicals in normal brain functioning has not been well characterized. However, recent studies have found that neurometabolic concentrations assessed within a voxel of occipital–parietal white matter were independently associated with intellectual and neuropsychological functioning in a cohort of normal college-aged students (Jung, 1999). In the current study we wanted to explore the relationship between neurometabolism and mood. Specifically, we hypothesized that neuronal metabolites in normal individuals would be significantly related to measures of positive and negative affect. Second, given the established importance of left frontal lobe integrity to affective disorders, we hypothesized that left frontal spectroscopy would be most sensitive to subtle variations in mood.

Methods

Subjects. Twenty-five participants (10 female, 15 male) were recruited from the local college community. Informed consent was obtained from all participants prior to study under a protocol approved by the Institutional Review Board. Participants were screened to exclude obvious organic or medical disease known to affect neurochemistry and mood: prior traumatic brain injury, disorders of attention, learning disability, neurological disease, psychiatric diagnosis, and use of psychoactive medications. Spectroscopic data were available on 24 of the 25 subjects due to technical issues related to spectral acquisition.

Magnetic resonance imaging and spectroscopy. All MR acquisitions were carried out on a 1.5-T clinical MR scanner using standard software (GE Medical Systems, Waukesha, WI). Imaging included sagittal \(T_1\)- and axial \(T_1\)- and \(T_2\)-weighted series. A PRESS pulse sequence, including water suppression, was employed to sample three voxel locations (\(TE = 30\) ms, \(TR = 2000\) ms, 128 averages, 12.6 cm\(^3\)) within left occipitoparietal, left frontal, and right frontal white matter. Specific voxel locations were prescribed from a \(T_1\)-weighted axial imaging series and were localized to maximize white and minimize gray matter and ventricular contribution.

Mood measurement. The positive affect negative affect scale (PANAS) was utilized to assess mood (Watson, 1988). Numerous studies have indicated a two-factor structure of affect—positive and negative—that are largely independent of one an-
The PANAS is brief, easy to administer, internally consistent, largely uncorrelated, and stable over a 2-month time period. Normative data and factorial and external evidence of convergent and discriminant validity for the scales are also available. The PANAS is comprised of 20 items—10 items for each scale (Positive/Negative)—on which the subject ranks the degree to which adjectives apply to them (1 = ‘not at all’; 5 = ‘strongly’). Thus, the minimum score on either scale is 10, and the maximum score is 50.

Statistical analysis. Spearman correlation coefficients were created to assess the initial relationships between affect (positive and negative) and metabolites (Cho, Cre, NAA) within the three voxel locations (left occipital, right frontal, left frontal). Linear regression models were used to assess potential predictors of positive and negative affect, the dependent variables. Independent variables were neurochemical concentrations of NAA, Cho, and Cre within the three voxel locations—left frontal, right frontal, and left occipital. Statistical analysis was conducted in SPSS for Macintosh (SPSS Inc., 1995).

Results

Complete spectroscopy and PANAS measures were obtained from 24 experimental subjects (10 female, 14 male). Mean age for the sample was 23.4 years ± 4.7. Mean scores for Positive Affect were (33.40 ± 3.63), and for Negative Affect were (14.40 ± 6.34). Negative Affect was strongly skewed to the low end of the scale, while Positive Affect was normally distributed. Age was significantly correlated with metabolic measures, particularly Cho in the right frontal (r = .46, p < .05) and left occipital (r = .51, p < .05) voxel. Consequently, age effects were accounted for (partialed out) in initial correlation coefficients and in the final regression equation.

In our initial analysis, we found that spectroscopic measures were significantly correlated with measures of Positive Affect after controlling for age effects. Specifically, Cho was inversely correlated with measures of positive affect in left frontal (r = −.76, p < .04), right frontal (r = −.50, p = .014), and occipital cortices (r = −.43, p < .001). Negative Affect was not significantly correlated with any spectroscopic measure. Cre was significantly correlated with Positive Affect within the left frontal lobe only (r = −.50, p = .014) and was not correlated with Negative Affect.

To assess the regional contribution of neurometabolites to affect, we regressed all neurometabolites from all voxel locations and age against Positive Affect, the dependent variable. We found that a model including only left frontal Cho best predicted Positive Affect in our experimental sample (F = 31.31, p < .0001). Thus, left frontal Cho could account for well over 50% of the variance in Positive Affect (r² = .59).

Discussion

This research establishes the first finding of 1H-MRS neurometabolic differences related to mood functioning in a cohort of normal young subjects. While the PANAS is not a measure of mood dysfunction per se, it does tap the fundamental attributes of normal and pathological mood states and correlates well with other measures of mood including the Beck Depression Inventory and the Symptom Checklist–90. This experimental relationship between left frontal lobe Cho and Positive Affect is consistent with previous research demonstrating left frontal lobe derangement in a wide range of mood disorders. Similarly, elevated Cho has been reported to be inversely correlated to intellectual functioning in a cohort of normal subjects (Jung, 1999). Thus, it is possible that elevated Cho may reflect increased cellular membrane turnover secondary to metabolic stress or other neurometabolic factors. Future research
will be critical to: (1) confirm these findings in a larger cohort, (2) establish the role of Cho in more overt mood disorders and symptomatology across the clinical and subclinical continuum, and (3) establish the variability of the Cho resonance in the presence of fluctuations in mood states.

REFERENCES


18. Functional Magnetic Resonance Imaging and Event-Related Potentials Suggest Right Prefrontal Activation for Self-Related Processing

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Research has indicated that self-related processing may be subserved by a cortical network within the right prefrontal cortex (RPFC). These indications are derived from case studies as well as functional neuroimaging data in which self-related stimuli appear to activate cortical structures within the RPFC. To extend these findings we employed self-faces as stimuli. Under two experiments, one using fMRI (functional magnetic resonance imaging) and the other employing ERPs (event-related potentials), subjects were presented with self-faces under two slightly different paradigms. Preliminary data from both fMRI and ERPs indicate that self-face perception and self-processing may involve preferential circuits within the RPFC. These data support the notion that there may be right frontal lateralization for self-related processing.

It has been speculated that self-awareness may be a precursor to higher-order abstract cognitive processes. While there are indications that cognitive self-representation engages the right prefrontal cortex (RPFC) preferentially, the data are far from complete. Craik and colleagues (1999), employing positron emission tomography (PET), presented subjects with an adjective list and asked the subjects in one condition to decide if the words described themselves and in the other condition, to decide if the words described a famous person. Greater activity was found in the RPFC when subjects were making self-related judgments compared to the famous and a series of baseline conditions. Levine et al. (1998) found that damage to the RPFC led to the loss of episodic and autobiographic memories in a patient. These data, as well as examinations by others, support the notion that self-related cognitive processing is correlated preferentially with cortical networks involving the RPFC (Wheeler, Stuss, & Tulving, 1997). These results may be extended to a general self-
related hierarchy, described by Stuss in which the frontal lobe appears to play a critical role (Stuss & Benson, 1986).

To extend these findings, we presented subjects with self-faces under two conditions using both fMRI (functional magnetic resonance imaging) and ERPs (event-related potentials). In the fMRI study, subjects were presented with self- and famous (Bill Clinton) faces accompanied with descriptive text. In the ERP study, self-faces were presented among a series of familiar faces. In a second condition, familiar faces were presented among famous faces. If self-related phenomena are truly mediated by RPFC activity, we predicted that this region would be significantly more active under conditions of self compared to famous (fMRI) or familiar (ERP).

Experiment 1

Methods

The goal of Experiment 1 was to determine if the presentation of self-related material would activate a common neural substrate when compared to non-self-related stimuli. The two subjects tested were right-handed and reported no neurological trauma. Subjects were first prescreened as to their ability to attend to, and not be overly emotional about, the stimuli. Subjects viewed stimuli with accompanying text, with four descriptors such as ‘I think,’ ‘I believe’ (or ‘He thinks,’ ‘He believes’). Descriptors and pictures were changed for each presentation. Various pictures were used, categorized into those of the subjects’ faces and those of Bill Clinton. Subjects were shown each image with the four lines of text under each picture for a total of 30 s each. A total of 32 presentations were made per subject (16 Self, 16 Famous). Subjects were instructed to, at their leisure, alternate between the images and the descriptive statements and informed that they would be asked questions following scanning. A recall task and debriefing, following scanning, were performed.

All functional studies were performed on a conventional 1.5-T GE Signa scanner. A 3D Presto pulse sequence was implemented. One functional volume consisted of 24 slices. Cubic voxels of 3.75 mm³ were obtained. Anatomical data was acquired as a T1-weighted MRI scan. Depending upon the subject’s anatomy, 24 to 31 slices of 256 × 256 pixels each were obtained. Voxel sizes of 0.9 × 0.9 × 3.80 mm were maintained. After acquisition, raw data were transferred to an offline workstation for reconstruction and analysis. Reconstruction was performed on a Sun-SPARC workstation using IDL processing software. The automated image registration (AIR 3.02) software was used for image registration. Data processing and analysis were performed with in-house software on an Indy workstation running IRIX 5.3. Contrasts were corrected for pixel comparisons and data was Bonferroni adjusted at the .05 level.

Results

In both subjects, the right inferior frontal gyrus in the triangularus was found to be activated (Fig. 1). It appeared that this region was on the border of the medial frontal gyrus in both subjects. Activations were anterior to the opercular regions of the inferior frontal gyrus. One subject (No. 2) had significant occipital activations, located in the occipital gyri and the gyri of the superior parietal lobe. This subject also had left striate activation, as well as activation in the left posterior parietal cortex. Further, the frontal activation in this subject appeared more dorsal as well, extending in the medial frontal gyrus on the right. No limbic activity was observed to be significant in either subject.
FIG. 1. Example of stimuli for Self and Famous presented (top center). Statistical maps displayed for two individual subjects. Data are comparison between Self and Famous, with activations delineating significant pixel activation ($p < .05$, Bonferroni adjustment). Inserts indicate regions similarly activated in both subjects.

Experiment 2

Methods

Six right-handed subjects were tested. All were right-handed and all were screened for neurological trauma. Faces of each of the participants were prepared as described previously (Keenan et al., 1999). Subjects were run in pairs, such that Subject 1 was presented with the face of Subject 2, and Subject 2 was presented with the face of Subject 1.

Two conditions were carried out. In the first ‘Self’ condition, 500 faces were presented (500-ms display, 500-ms ISI). The Self-faces were presented 20% of the time (100 pictures). The remaining photographs were those constructed similarly as the self-face, of Bill Clinton, Marilyn Monroe, Albert Einstein, and Princess Diana (100 presentations each). All photographs were presented randomly. In this first condition, subjects were instructed to silently count the number of times that they viewed their own face (display and distance, see Keenan et al., 1999). The second condition was similar to the first, with the exception of the Self-face being replaced by a Familiar face. The familiar face was a co-worker of at least 1 year. The task in this condition was for the subject to count the number of times the familiar face was presented. The order of the conditions was counterbalanced.

Subjects were fitted with a standard nine-channel system frontal montage at positions Cz, Fz, Fp1, Fp2, F3, F4, F7, F8, and A1 (linked reference). Frontal locations were chosen based on previous findings, and a limited field was employed so that statistical comparisons could be maximized. Impedance was defined at 3 kOhm; the
rejection limit was +45 mV. Sampling was set at 1000 Hz. Only the P300 was scored, determined as the first positive wave ± 1 SD 300 ms. All analyses were performed with NeuroScan v.4.0 and SPSS for Windows v.9.0

Results

Amplitude. Within the Self-group, a significant difference emerged in two regions: F8 and CZ. It was found after comparing all electrodes (except CZ) that the amplitude of the P300 was significantly increased for F8 ($p < .05$) and CZ ($p < .05$; F8 vs CZ was nonsignificant). Within the Familiar group, a significant increase against all other electrodes was found in the region of F7 ($p < .05$).

Two significant effects were found for individual electrode comparisons between Self and Familiar conditions. There was an increase at area F8 ($p < .0005$; Self > Familiar). There was also a significant decrease in area F7 ($p < .01$; Self < Familiar). All other comparisons were nonsignificant ($p > .05$).

Latency. Within-condition contrasts were all nonsignificant. For the between-condition contrasts, it was found that there was a significant difference at location F8 ($p < .005$; Self < Familiar). Conversely, a significant increase was detected over area FZ ($p < .05$; Self > Familiar). All other comparisons were nonsignificant.

General Discussion

For both the fMRI and the ERP study, self-related stimuli activated the RPFC preferentially. While both studies are reports of preliminary data, the results thus far support previous research which has indicated RPFC activations for self-stimuli (Levine et al., 1998; see Wheeler et al., 1997). Given that the RPFC has been previously indicated as mediating self-face recognition (Keenan et al., 1999), we are further encouraged by the data. Caution should be taken with the interpretation of these results. For example, effects for familiarity, novelty, and attention may have contributed to the activation patterns observed. Also, both sample sizes are low. Further studies should address these issues.

Given however these qualifications, the data are in agreement with neuroimaging studies that have employed other self-related stimuli. Further, the specific region of activity within the fMRI experiment is quite similar to that of the lesion described by Levine et al. (1998). This patient had intact anterograde memory, yet experienced significant difficulty in episodic, personal memory tasks. While the specificity of the ERP is more difficult to discern, self-face recognition does appear to preferentially activate this region during a similar task.

It is possible that internally generated representations are modulated according to the hierarchy of self-awareness postulated by Stuss and Benson (1986). According to this theory, executive processing incorporates internally driven anticipation, planning, and monitoring. The core of these processes is the internal, executive ‘self’ (Wheeler et al., 1997). Damage to the right hemisphere, which appears to disrupt various components of this hierarchy (Levine et al., 1998) may be thought of in terms of executive dysfunctions, rooted in an internal self-monitor. Recognition of self may also be mediated by such an internal monitor. Though speculative, this hypothesis is certainly worthy of further examination.

REFERENCES


19. A fMRI Study of Frontal Lobe Functioning during Emotional Processing

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This study investigated neuronal response in the frontal lobes during the emotional processing of faces and pictures in young adults. fMRI BOLD signals were obtained while participants performed implicit or explicit emotional processing tasks. Linear contrasts were specified using SPM to compare patterns of brain activation. We expected that explicit emotional processing would be accompanied by increased frontal activation. This assertion was supported by observing the activation patterns localized to Brodmann areas 8 and 32, although this effect was mainly seen for pictures. © 2001 Academic Press

The frontal lobes contribute to the experience of emotion and affective style. Neuroimaging studies of depressed individuals consistently reveal a decrease in frontal lobe metabolism. In addition, when a sad mood is induced and maintained in healthy individuals, blood flow decreases in the prefrontal areas (Mayberg, 1997). The frontal lobes may play a role in the conscious experience of emotion or emotion-related decision making (Lane et al., 1997).

Lane, Fink, Chau, and Dolan (1997) measured regional cerebral blood flow (rCBF) while healthy males judged pictures either to evoke a pleasant, unpleasant, or neutral feeling (internal condition) or to take place indoors, outdoors, or both (external condition). During the internal conditions there was significantly increased rCBF to the anterior cingulate, which extended into medial prefrontal areas. The authors concluded that the evaluation of the emotional significance of a novel stimulus may involve a reference to a previous experience which may be mediated by anterior prefrontal regions, a process which could also be conceptualized as a reference to the self.

The self-referential process is considered to be a component of episodic memory and has been investigated in a recent PET study that compared neural activation in self-referential encoding versus general semantic and nonsemantic encoding (Craik et al., 1999). Participants were scanned while deciding if a trait described the self, described someone else, whether the trait was generally desirable, or while counting the number of syllables it contained. The differences between semantic conditions were minimal, but judging the trait to describe one’s self increased activation in the medial prefrontal cortex (BA 8/9) and inferior frontal gyrus (BA 45) compared to counting the number of syllables. Reference to the self may thus involve a conscious affective component, which would account for activation in regions similar to those active during emotional processing.

The present study was performed to test the hypothesis that significantly increased activation will occur in the prefrontal cortex while explicitly evaluating the emotional significance of faces and pictures, but not while performing a visual discrimination.
task (implicit emotional processing). We also wanted to determine if explicit emotional processing engaged the same or different areas for the two types of stimuli.

**Method**

Scanning was performed on 10 young participants (5 male, 5 female; mean age 23 years). Stimuli consisted of emotionally positive, negative, or neutral faces and pictures. Participants performed an implicit or explicit emotional processing task or were instructed to view neutral stimuli passively. In the implicit task, participants identified the gender of the face or counted the number of people in the picture. In the explicit task they identified the affective valence of the face/picture as positive or negative. At the end of the experiment, participants were also tested for recognition of previously presented positive and negative stimuli.

T1-weighted anatomical volumetric images (SPGR 0.8 × 0.8 × 1-2 mm voxels) and T2*-weighted images (EPI, TE = 40 ms) with blood oxygenation level-dependent (BOLD) contrast were obtained using a whole-body MRI scanner operating at 1.5 T (GE Medical Systems). EPI acquisitions normally consisted of 17 axial slices 7 mm thick taken every 3 s, positioned to encompass the whole brain. Data were processed using SPM99b and linear contrasts were specified to compare patterns of brain activation.

**Results**

The contrast of explicit versus implicit processing tasks (collapsed across both faces and pictures) significantly increased activation in the medial prefrontal cortex (BA 8, p < .001) and anterior cingulate gyrus (BA 32, p < .01). This effect (see Fig. 1) was mainly seen for pictures, as contrasting explicit and implicit picture processing also resulted in significantly increased activation of the medial prefrontal cortex (BA 8, p < .001) but explicit face processing did not. The contrast of pictures

![FIG. 1. A statistical parametric map illustrating medial prefrontal activation during explicit versus implicit emotional processing. An uncorrected p value of 0.01 was used as the threshold for the contrast. Views of the brain are shown for orthogonal slices. The significant areas of activation are displayed on a mean structural MRI.](image-url)
versus faces in the recognition condition resulted in a significant increase in activation in the medial prefrontal cortex (BA 8, \( p < .05 \)).

**Discussion**

In support of the initial hypothesis, the medial prefrontal cortex was significantly activated during the explicit versus the implicit emotional processing task. However, this effect was only statistically significant (when corrected for multiple comparisons) for the explicit picture condition. It is not clear why this effect was not found for faces, but it could be related to the increased visual complexity of the pictures, which may result in more elaborate evaluation of the emotional significance due to a greater context for interpretation. A PET study performed by Lane et al. (1997) also found increases in medial prefrontal regions and anterior cingulate when participants viewed pleasant and unpleasant pictures compared to neutral pictures.

Interpreting the emotional significance of a picture (compared to a face) may be more likely to activate a self-referential process in which the prefrontal cortex is involved in representing conscious awareness of affect. In contrast, the implicit emotional processing task did not require participants to focus on the meaning of the picture. They could successfully perform the task by filtering out the context and counting the people. Perception of emotion in a face may be more automatic than for pictures, thus not requiring the frontal area.

The increased activation in the medial prefrontal cortex found by contrasting the encoding and recognition of emotional pictures versus emotional faces suggests that the emotional processing of sufficiently complex novel stimuli (e.g., pictures) may be similar to the process during episodic encoding and retrieval when task instructions require self-referential comparisons. This suggests a close correspondence between emotional processing and self-reference that deserves further study.

**REFERENCES**


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20. **Dissociating the Functional Properties of the Medial and Lateral Anterior Prefrontal Cortex**

**E. Koechlin,** G. Corrado, P. Pietrini, and J. Grafman

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The anterior prefrontal cortex (APC) is known to subserve higher cognitive functions like planning. However, little is known about the functional specialization within this region in humans. Using functional magnetic resonance imaging we report a double dissociation: the medial
APC and the ventral striatum were engaged when subjects executed tasks in sequences that were fixed, whereas the polar APC and dorsolateral striatum were involved in task sequences that were contingent upon unpredictable events. These results parallel the functional segregation previously described in the premotor cortex suggesting common frontal organizational principles underlie motor and higher executive functions in humans. © 2001 Academic Press

Introduction

The anterior prefrontal cortex in humans is known to subserve higher cognitive functions, including planning. In particular, the anterior prefrontal cortex was shown to be selectively engaged when subjects were required to hold in mind a primary goal, while performing sequences of intermediate tasks (Koechlin, Basso, Pietrini, Panzer, & Grafman, 1999). However, little is known about the functional specialization within the anterior prefrontal cortex.

Several theoretical studies have emphasized a conceptual distinction between predictive and reactive planning (Spector & Grafman, 1994). In predictive planning, subjects perform a fixed sequence of intermediate tasks in route to completing a primary goal; i.e., tasks are executed according to a fixed procedure. In reactive planning, in contrast, intermediate tasks are executed in sequences that are contingent upon unpredictable events. Thus, in order to reach a primary goal, subjects perform, opportunistically, intermediate tasks depending on environmental contingencies.

In motor control, previous studies have revealed that performing fixed sequences of movements involved, preferentially, the medial premotor cortex, whereas performing movements in reaction to sensory events involved, preferentially, the lateral premotor cortex (Passingham, 1993). Thus, in the present study, we tested the hypothesis that predictive planning and reactive planning would involve distinct anterior prefrontal networks along a medial–lateral axis.

Methods

Using functional magnetic resonance imaging, six normal right-handed human subjects were tested, while they were performing sequences of matching tasks on series of visually presented letters by pressing hand-held response buttons. Subjects were required to repeatedly perform a primary task, but were occasionally cued to temporarily suspend, in midperformance, the primary task in order to complete intermediate tasks. This planning process was described in detail and has been shown to engage the anterior prefrontal cortex in (Koechlin et al., 1999).

In the reactive condition, intermediate tasks were contingent upon letter cues presented randomly. In the predictive condition, cues were presented at fixed times, so that intermediate tasks were performed in fixed sequences. Working memory load and task-switching demand remained similar in both conditions. Finally, in a control condition, subjects were asked to perform direct visuomotor associations on a continuously repeated six-letter sequence. Subjects were instructed about the informational structure of each testing block by visual signals presented right before the onset of each block.

The three conditions were administered using a Latin-square block design divided in six scanning runs. A high-resolution structural scan was performed for each subject followed by six functional scans (1.5-T GE Signa scanner, 128 axial volumes, TR 3 s, TE 40 ms, flip angle 90°, FOV 24 cm, acquisition matrix $64 \times 64$, number of slices 18, thickness 6 mm).

All fMRI data were processed using SPM96. Linear realignment, normalization, Gaussian spatial (FWHM, 10 mm), and temporal smoothing were successively per-
formed for each subject. Then, all subjects were pooled together and statistical parametric maps were computed using a linear multiple regression with conditions and runs as covariates. Only frontal and basal ganglia activations including more than 26 contiguous active voxels ($p < .05$) were analyzed.

**Results**

We first investigated brain regions involved in *both* planning conditions relative to baseline by selecting voxels with significant activations in both experimental conditions collapsed together compared to baseline ($Z > 4.2, p < .05$, corrected for the number of tested voxels in the frontal lobes) and with significant activations in each planning condition compared separately to baseline ($Z > 3.09, p < .001$, uncorrected). This analysis revealed activations located bilaterally in the medial and lateral premotor cortex (BA 6 and 44), the dorsomedial (BA 8), the mediopolar prefrontal cortex (BA 10), and the thalamus (see Table 1).

Second, we identified brain regions preferentially involved in *reactive* planning by selecting voxels with significant activations in the reactive compared to the predictive conditions ($Z > 4.2, p < .05$, corrected). Activations were located mainly in the bilateral frontopolar cortex (BA 10) and extended to the adjacent dorsolateral prefrontal cortex (BA 8/9/46). Bilateral premotor cortex (BA 6 and left BA 44), pre-SMA, ventral cingulate, and left dorsolateral striatum activations were also observed. All these active regions were also significantly active in the reactive condition when

<table>
<thead>
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<th>TABLE 1</th>
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<td><strong>Foci of Activations in the Frontal Lobes and Basal Ganglia</strong></td>
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<tr>
<th>Anatomical regions</th>
<th>Left</th>
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<tr>
<td><strong>Reactive &gt; predictive</strong></td>
<td></td>
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<tr>
<td>BA 10 frontopolar gyrus</td>
<td>$-18, 63, 15$</td>
<td>$24, 60, 18$</td>
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<tr>
<td>BA 9/46 middle frontal gyrus</td>
<td>$-30, 30, 36$</td>
<td>$36, 39, 30$</td>
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<tr>
<td>BA 8 superior frontal gyrus</td>
<td>$-12, 48, 30$</td>
<td>$24, 30, 42$</td>
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<tr>
<td>BA 44/45 inferior frontal gyrus L</td>
<td>$-57, 9, 15$</td>
<td>$57, 24, 18$</td>
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<tr>
<td>BA 6 pre-SMA</td>
<td>$-12, 21, 51$</td>
<td></td>
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<tr>
<td>BA 6 middle frontal gyrus</td>
<td>$-33, 9, 51$</td>
<td>$24, 9, 54$</td>
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<tr>
<td>BA 24 cingulate gyrus</td>
<td>$0, 18, 24$</td>
<td></td>
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<tr>
<td>Putamen</td>
<td>$-18, 6, 3$</td>
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<tr>
<td><strong>Predictive &gt; reactive</strong></td>
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<tr>
<td>BA 32/10 cingulate/medial prefrontal</td>
<td>$-9, 39, -6$</td>
<td>$9, 42, -6$</td>
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<td>Caudate/acumbens nucleus</td>
<td>$-12, 15, -9$</td>
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<td><strong>Predictive and reactive &gt; baseline</strong></td>
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<td>BA 10 frontopolar gyrus</td>
<td>$-6, 63, 24$</td>
<td>$15, 63, 21$</td>
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<tr>
<td>BA 8 superior frontal gyrus</td>
<td>$-12, 45, 39$</td>
<td>$9, 48, 39$</td>
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<tr>
<td>BA 44 inferior frontal gyrus</td>
<td>$-60, 3, 21$</td>
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<tr>
<td>BA 6 SMA</td>
<td></td>
<td>$12, -9, 66$</td>
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<tr>
<td>BA 6 pre-SMA</td>
<td></td>
<td>$6, 3, 57$</td>
</tr>
<tr>
<td>BA 6 middle frontal gyrus</td>
<td>$-45, -3, 45$</td>
<td>$36, 3, 51$</td>
</tr>
<tr>
<td>Thalamus</td>
<td>$-9, -9, 12$</td>
<td>$6, -6, 9$</td>
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compared to baseline ($Z > 3.09, p < .001$, uncorrected). Among those regions, the premotor, dorsomedial and mediopolar prefrontal regions were also activated in the predictive conditions relative to baseline as described above. In contrast, neither the bilateral frontopolar regions nor the dorsolateral striatum were found to be significantly activated in the contrast predictive minus baseline ($Z < 1.7, p > .05$, uncorrected).

Third, we examined regions involved preferentially in predictive planning by selecting voxels with significant activations in the predictive compared to the reactive conditions ($Z > 4.2, p < .05$, corrected). Activations were located bilaterally in the anterior medial prefrontal/cingulate cortex (BA 32/10) and in the left ventral striatum (acumbens nuclei). All these regions were also significantly active in the contrast predictive minus baseline ($Z > 3.09, p < .001$, uncorrected) and none were found to be involved in the contrast reactive minus baseline ($Z < 1.7, p > .05$, uncorrected).

**Discussion**

The present results confirmed the predicted functional dissociation within the anterior prefrontal cortex. Relative to baseline, the lateral anterior prefrontal cortex was engaged only when subjects executed intermediate tasks in sequences that were contingent upon unpredictable cues. In contrast, the medial anterior prefrontal cortex was significantly involved only when subjects executed intermediate tasks in sequences that were previously set.

Behavioral performance provides evidence that those distinctive patterns of activation were unlikely to result from variations of mental effort alone across conditions. In addition, previous studies rule out the interpretation that lateral anterior prefrontal activations reflect conditional statements (i.e., “if–then” statement) or contingent task-switching processes alone (D’Esposito et al., 1995; Koechlin et al., 1999). Therefore, we conclude that lateral frontopolar regions subserve, specifically, processes underlying reactive planning, allowing primary goals to be temporarily held and sequences of intermediate tasks to be executed in reaction to unexpected events. Conversely, the results show that the anterior medial prefrontal cortex is specifically involved when sequences of primary and intermediate tasks are performed according to a previously set plan.

Moreover, the anterior medial prefrontal activations reported here were accompanied by activations in the ventral striatum, whereas the anterior lateral prefrontal activations were accompanied by dorsolateral striatal activations. In agreement with our results, the ventral striatum is known to receive, preferentially, projections from the medial prefrontal cortex, while the dorsal striatal regions are preferentially connected to the lateral prefrontal cortex. Moreover, neurons in the ventral striatum were shown in monkeys to process expectations and to encode progress in previously set behavioral plans.

In summary, our results reveal two functionally segregated frontostrial networks within the anterior frontal lobes based on the conceptual distinction between predictive and reactive planning (Spector & Grafman, 1994). This finding identifies distinct information processing for the previously described medial and lateral frontostrial anatomical circuits that project from and to the anterior prefrontal cortex (Alexander, DeLong, & Strick, 1986). Furthermore, these findings broaden the previously reported functional division within the premotor cortex between internally and externally driven motor sequences (Passingham, 1993), to high-level planning and task management. This suggests that common frontal organizational principles underlie motor and higher executive functions in humans.
REFERENCES


21. Activity in Medial Prefrontal Cortex Correlates with Vagal Component of Heart Rate Variability during Emotion

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To explore the neural substrates of autonomic regulation during emotion, we correlated the vagal [high frequency (HF)] component of heart rate variability (HRV) with cerebral blood flow in a PET ¹⁵O–water study in 12 healthy women. Happiness, sadness, disgust, and three neutral conditions were each induced by film and recall of personal experiences (12 conditions). Interbeat intervals during scans were spectral analyzed, generating 12 measures of HF-HRV in each subject. Correlations between HR-HRV and rCBF specifically due to emotion were observed in medial prefrontal cortex ($Z = 3.20, p < .001$) and left posterior orbitofrontal/anterior insular cortices ($Z = 3.58, p < .001$). These findings are consistent with an inhibitory role of prefrontal cortex and evidence that the anterior insular cortex and medial prefrontal cortex participate in visceral interoception and autonomic regulation. © 2001 Academic Press

Introduction

Research on the neural substrates of emotion in healthy volunteers is at a relatively early stage of investigation. One key question is how autonomic functions are regulated during emotional arousal. Most of what is known is based on studies in animals and patients with brain lesions. This study is among the first to examine the neural substrates of autonomic control during emotional arousal in healthy subjects.

We examined the high frequency (HF) component of heart rate variability (HRV), an index of vagal tone. This physiological measure is an important index of cardiovascular regulation in both normative and clinical contexts. This component of HRV is considered to reflect vagal antagonism of sympathetic influences and is a known predictor of survival in postmyocardial infarction patients.

Methods

Positron emission tomography (PET) and ¹⁵O–water were used to measure cerebral blood flow in 12 healthy women. Happiness, sadness, disgust, and three neutral conditions were each induced by film clips and recall of personal experiences (12 conditions). The six emotion and six neutral conditions were grouped together in this analysis.
ECG (lead II) was recorded during each 1-min scan. Consecutive RR intervals were measured by hand. A spectral analysis of interbeat intervals was performed in a separate laboratory. A fast Fourier transform was used to generate the heart period power spectrum. The HF component (0.15–0.40 Hz), the purely vagal respiratory component of HRV, can be reliably measured over 1-min epochs. Twelve separate measures of HF-HRV were obtained in each subject.

A multivariate analysis was performed in SPM96. Regional CBF was adjusted for global blood flow on a subject-specific basis. HF-HRV was entered as a covariate of interest. We report correlations between HF-HRV and rCBF specifically attributable to emotion (emotion minus neutral) as well as correlations between HF-HRV and rCBF during the emotion and neutral conditions separately.

Results

HF-HRV values tended to be lower during the emotion compared to the neutral conditions. HF-HRV values associated with the emotion-evoking films were significantly lower than those during the neutral films ($p < .05$); this was true for the happy film in particular compared to the neutral films ($p < .05$). The disgust recall condition was associated with lower HF-HRV values than the neutral recall conditions ($p < .05$). These trends and significant findings were all in the predicted direction. There was marked variability of HF-HRV values within each condition, precluding statistical significance in many categories in this small sample but very suitable for a covariance analysis.

Compared to the neutral conditions all emotion conditions were associated with activation of superior medial prefrontal cortex. The recall conditions were associated with activation of the left insula. A baseline condition to detect activation during neutral conditions was not included in the design of this study. Complete reports of the PET findings associated with the different emotions and stimulus modalities have been published previously.

During the emotion conditions HF-HRV correlated with rCBF in medial prefrontal cortex (coordinates, $-8, 52, 30; Z = 3.40, p < .001$) and in the region of left orbitofrontal and anterior insular cortices (coordinates, $-46, 24, 2; Z = 3.53, p < .001$). During the neutral conditions HF-HRV correlated with rCBF in right inferior frontal cortex (coordinates 20, 48, 6; $Z = 3.44, p < .02$, corrected) and brain stem (inferior pontine tegmentum) (coordinates, $-6, -22, -24; Z = 3.18, p < .001$). Correlations between HR-HRV and rCBF specifically due to emotion (emotion minus neutral) were observed in medial prefrontal cortex (coordinates, $-8, 56, 30; Z = 3.20, p < .001$) (see Fig. 1) and left posterior orbitofrontal/anterior insular cortices (coordinates, $-50, 24, 8; Z = 3.58, p < .001$).

Discussion

During the neutral states the right inferior frontal cortex and inferior pontine tegmentum are preferentially involved. The SA node, which controls heart rate in the right atrium, is under right-sided vagal and sympathetic control. Greater decreases in HRV are present in patients with right compared to left hemisphere strokes (Naver et al., 1996). This region of inferior frontal cortex is a “watershed area” where the distributions of the anterior and middle cerebral arteries overlap. During episodes of compromised cardiac output this is an area that is vulnerable to infarction due to ischemia.

The inferior pontine tegmentum is at the pontomidbrain junction. It is therefore unlikely to reflect activity in vagal nuclei. In the context of emotionally neutral stimuli
FIG. 1. A statistical parametric map (SPM) superimposed on the average structural MRI of the 12 female subjects. This figure demonstrates a statistically significant positive correlation in medial prefrontal cortex (coordinates, $-8, 56, 30; Z = 3.20, p < .001$) between increases in rCBF attributable to emotion and the high frequency component of heart rate variability.

the increased activity in this region may reflect activity in the reticular system. We speculate that in the neutral state arousal mechanisms and vagal inhibitory influences are in balance and simultaneously activated.

During emotional states the medial prefrontal cortex and left posterior orbitofrontal and anterior insular cortices are preferentially involved in regulating vagal tone. Stimulation of the medial prefrontal cortex is known to produce decreases in heart rate and blood pressure in rabbits (Buchanan et al., 1985). In the context of emotional arousal, the medial prefrontal cortex may be a staging area for integrating interoceptive and exteroceptive information for the purpose of generating goal-directed behavior. Heightened vagal activity may reflect inhibitory processes associated with the selection of an action disposition.

Another area preferentially associated with HF-HRV during emotion was a region that included the left anterior insula/posterior orbitofrontal cortex. Stimulation of each structure is known to produce autonomic changes. In five epileptic patients, stimulation of left insular cortex produced bradycardia and depressor responses, whereas right insular stimulation produced increases in heart rate and blood pressure (Oppenheimer et al., 1992). Phasic stimulation of rat insular cortex resulted in heart block, QT prolongation, ventricular ectopy, and sudden death (Oppenheimer et al., 1991). Thus, the current findings are consistent with other human data and support the hypothesis that activity of the anterior insular cortex influences vulnerability to sudden cardiac death.

In the context of coronary artery disease depression is associated with an increased incidence of sudden death. Depression is also associated with decreased HRV. Decreases in rostral anterior cingulate/medial prefrontal cortex have been observed in depressed patients at rest (Mayberg et al., 1997). In light of the present findings, dysfunction of this region in depression may be associated with a relative inability to recruit this region and its associated influence on vagal control.

Conclusions

The cerebral structures that participate in vagal control of heart rate vary as a function of mental state. During neutral states the right inferior frontal cortex and inferior pontine tegmentum are preferentially involved.

During emotional states the medial prefrontal cortex and left posterior orbitofrontal and anterior insular cortices are involved. Further research is needed to determine whether the current findings reflect activity of sensory or motor vagal processes or
Research demonstrating the cardiovascular effects of electrical stimulation of these structures suggests that these correlations reflect direct physiological influences in autonomic control.

The present findings are consistent with an inhibitory role of medial prefrontal cortex, evidence in rodents that lesions in medial prefrontal cortex are associated with prolonged extinction of conditioned fear, and evidence that the anterior insular cortex and medial prefrontal cortex participate in visceral interoception and autonomic regulation.

Both the medial prefrontal cortex and the anterior insular cortex were activated during the emotion relative to the neutral conditions. Additional research is needed to determine whether these activations reflect their participation in autonomic control exclusively or whether these areas serve multiple functions simultaneously in the mediation of emotional responses.

REFERENCES


22. Prefrontal Modulation of Limbic Activation during an Emotional Functional Magnetic Resonance Imaging Task

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Introduction

The biological substrates of emotion are poorly understood. Functional magnetic resonance imaging (fMRI) offers the researcher the ability to investigate in vivo neural activation, as induced by changes in magnetic susceptibility caused by changes in oxygen content. Past studies have indicated a right-hemispheric bias in processing...
negatively valenced emotions. For example, Canli et al. (1998) used fMRI in a study of 14 female subjects viewing alternating blocks of emotionally valenced positive and negative pictures. When the valence was equated for arousal, overall brain activity was lateralized toward the left hemisphere for positive pictures and toward the right hemisphere for negative pictures. In a study of the neural substrates underlying processing of emotion-related meanings, Teasdale et al. (1999) examined 6 healthy subjects while viewing alternating blocks of pictures and captions that evoked either negative feelings or the same materials irrelevantly paired to produce less emotion as reference pairs. Compared with the baseline picture–caption pairs, negative pairs activated the right medial and middle frontal gyri, right anterior, cingulate gyrus, and right thalamus. Similarly, Beauregard et al. (1998) had normal and depressed subjects view emotionally laden and neutral films. Results showed that sadness produced significant activation in the medial and inferior prefrontal cortices, the middle temporal cortex, the cerebellum, and the caudate in both groups. The amygdala is thought to be the seat of inner-emotional production, particularly negative emotions. The prefrontal cortex (PFC) with its connection to the amygdala is thought to act to inhibit the production of emotional responses. Dysfunction in response inhibition is seen in various psychiatric disorders with inappropriate emotional reaction such as depression, bipolar disorder, and obsessive–compulsive disorder.

The lack of consistent amygdala activation in the literature is possibly due to the presentation of stimuli, with affect then being applied. As studies used external application of affect, they may have elicited activation of substrates involved with the interpretation of stimuli, which may be subjectively interpreted as emotionally valenced. Few reports exist on the self-induction of emotional state without the influence of external stimuli. The study described here involved alternating conditions of self-generated loss induction and neutral states during fMRI data collection in normal adults. We hypothesized that the amygdala–hippocampal complex would activate with the emotional stimuli and that the prefrontal cortex would activate with attempts to inhibit the generated mood. Elucidating the neurobiology of mood induction is especially critical in advancing our understanding of mood disorders as the above-mentioned areas are thought to possibly mediate affective symptomatology (for a review see Drevets, 1999).

Methods

Subjects. The subject group consisted of normal adult volunteers, four females and four males. All subjects were right-handed. Group demographics were as follows: age (in years) 38.33 ± 7.91 (28.00–49.33), height 67.58 ± 4.30 in. (61–73 in), and weight 74.25 ± 21.20 kg (42–104 kg). Males did not differ from females on demographic variables such as age (males, 38.56 ± 8.02 years; females, 38.10 ± 9.03 years, t(3) = 0.730, p = .52), height in inches (males, 70.78 ± 2.58; females, 64.38 ± 3.04, t(3) = 2.997, p = .06), and weight in kilograms (males, 88.75 ± 14.73; females, 59.75 ± 16.48, t(3) = 2.153, p = .12).

Protocol. The paradigm was as follows: a baseline period was followed by incrementally increasing periods of loss induction (2, 3, 4, and 5 min), which alternated, with periods where the subjects were cued to return to a neutral emotional state. A Siemens Magnetom Vision MR scanner was used. Data collected were as follows.

Scout series. Standard FISP/GRASS sequence: TE = 6 ms, TR = 15 ms, alpha = 30°, slice thickness = 5 mm, FOV = 220 mm. Anatomical: 3D, T1-weighted MPRAGE (magnetization prepared rapid acquisition gradient echo), cubic voxels = 1.72 × 1.72 × 1.72 mm, matrix = 128 × 128, FOV = 220 mm, TR = 9.7 ms, TE = 4.0 ms, alpha = 12°. Functional: gradient recalled echo–echoplanar imaging (GRE-
FIG. 1. (A) Amygdala activation during the “loss” period and (B) prefrontal activation during the inhibition period between “loss” periods.

EPI) sequence with TE = 61 ms, TR = 8.16 s, 64 × 128 matrix, FOV = 220 mm. Whole brain imaging was performed collecting 16 axial slices, 5 mm thick, with a 1-mm gap between slices.

Results

During the loss period, subjects exhibited right-biased amygdala/hippocampal activation. Interestingly, during the rest periods when the subjects were instructed not to contemplate the loss, prefrontal cortex (PFC) exhibited activation (see Fig. 1). Both males and females demonstrated PFC activation, but females were more lateralized in amygdala activation (right bias). One subject (male) had a scan of particular note. On the day of the scan, the subject received word of a close relative passing away. The subject had previously chosen a particular emotional memory to utilize in the scan, but felt that it was failing to induce emotion. For the last two periods of loss, he switched to the thinking about the newly learned loss. During the first two periods of loss, very little signal change was noted. However, during the final two, after he switched to the fresh memory, the signal activation became very visible. Perhaps all his “affective resources” were in essence allocated to this new, fresh stimulus, and the previous stimuli lessened in emotional valence. A female subject had an initial adverse reaction to the cramped conditions of the scanner and had to cease the scan. She decided, under no coercion, to try again and succeeded in completing the experiment (she has actually participated in further studies). This particular subject’s data may be colored by anxiety more so than affect (loss) and may confound the interpretation of the data. The subject’s choroid plexus was actually visibly activated. The choroid plexus is highly vascularized and provides a route of transport for blood in situations when additional blood is needed by tissue. This may reflect the subject’s state of high arousal due to a distaste for scanner conditions as it was not evident in the further study (a finger tapping task).

Discussion

This fits with the proposed inhibitory role of the PFC over the amygdala. The degree of activation seemed to fit with the subjects’ subjective interpretation of their
own ability to elicit an emotional response in the scanner (i.e., greater emotional response in turn leads to a greater PFC response). The sex difference is consistent with the activation of the right amygdala for negative emotional stimuli; however it does conflict with some studies, but again, methodological differences have profound effect on fMRI studies and may account for the differences. As the technique evolves, more accurate replication and extension studies may begin to appear. Although the subjective nature of the subject’s perception and induction of arousal place limitations on the validity of the paradigm, this study demonstrates the utility of fMRI in the study of emotion, particularly in the study of mood disorders. Future directions include modifying the paradigm to include a neutral memory in place of “resting” condition to control for activation due to episodic memory as well as application to mood disorder patients. As the paradigm is refined it may also be used in studying emotional development in normal children and adolescents.

REFERENCES


23. Cortical Activity Associated with Attentional Interference Tasks

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This study compared the neuroanatomical substrates of two similar forms of interference effects, the attentional blink (AB) and the psychological refractory period (PRP), using fMRI. The task consisted of identifying two white targets (T1, T2), separated by either 200 or 600 ms, embedded in short streams of black letters. Common activations seen in both the AB and the PRP confirm premotor and cingulate involvement in attention tasks. Delay effects were seen in the prefrontal cortex and may be linked to a loss of processing efficiency observed in these interference effects at the short delays. Finally, the differences observed between the two tasks in medial prefrontal activity may be linked to the added masking interference in the AB effect.

Introduction

In rapid streams of visual stimuli, identification of a first target interferes with identification of a second target presented within the next second (Raymond et al., 1992). This outcome is generally referred to as the attentional blink (AB) and resembles another interference effect known as the psychological refractory period (PRP) (Pashler, 1992). Both are usually observed in dual tasks in which it is necessary to identify two targets that follow each other by less than 0.5 s. The two phenomena
are similar in many aspects, and only two points differentiate the PRP effect from the AB effect: (1) the PRP effect requires speeded responses to both targets; and (2) the targets are not masked by the distractors that follow them as in the AB effect. Various theoretical accounts have been proposed to explain both forms of interference; however, the neuroanatomical substrates of the AB and the PRP remain unknown. Human lesion studies have revealed that the frontal lobes may play an important role in both effects (Richer et al., 1997; Richer & Lepage, 1996). When compared to control groups, patients suffering from frontal lesions showed greater AB and PRP effects. Thus, it appears that the similarities between the AB and the PRP are not restricted to the methodology and may also be present at a neuroanatomical level.

The goal of the present study was to identify brain structures commonly activated by the AB and PRP effects, as well as those that differentiate between them, using functional magnetic resonance imaging (fMRI).

Methods

Subjects. Five healthy right-handed normal adults (three males, two females, mean age 25 years, range 22–34 years) participated in the study. Informed consent was obtained prior to scanning.

Task and procedure. The visual stimuli consisted of streams of uppercase letters (25-ms duration, 10/s) presented centrally on a visual display projected into the scanner via a pair of hood-mounted goggles (Resonance Technology Inc., Los Angeles, CA). In the experimental trials, all letters appeared black with the exception of two white targets, T1 and T2. T1 was the number 1 or 2, and T2 was the letter A or B. In each trial, T1 was preceded by zero to five letters and followed by three to nine letters. T2 followed T1 in one of two fixed positions so that either 200 or 600 ms separated the two targets. The distractors were chosen from a random letter sequence with the condition of no repetitions. Two task types were created: (1) streams of nine letters producing the AB effect; and (2) streams of nine letters in which the distractors immediately following T1 and T2 were removed and replaced by a 100-ms blank space to produce a PRP effect. This resulted in four trial types. A fifth trial type (control), a simple star in the center of the display which required no response, was also presented. A central fixation point (200 ms) indicated the beginning of a trial. Four-hundred milliseconds after the fixation point disappeared one of the five trial types was presented (900 ms). Trials were separated by 4.5 s.

Three different runs are were presented, each run containing 50 trials (10/trial type) in pseudo-random order. Subjects were instructed to identify a pair of targets T1 and T2, embedded in a series of black distractor letters, at the completion of each trial by pressing one of two response buttons. The order of runs was counterbalanced across subjects. Subjects carried out 24 practice trials prior to entering the scanner.

fMRI method and image analysis. Image acquisition was achieved using a Siemens Magnetom Vision 1.5-T MRI scanner with echoplanar imaging. One-hundred and sixty contiguous multislice $T_2^*$-weighted fMRI images were obtained for each run using an axial slice orientation (TE = 40 ms, flip 90°, TR = 2.0 s, 64 × 64 × 20 matrix size, $3.5 \times 3.50 \times 7$-mm voxels). The first 10 vol of each run were discarded leaving a total of 450 scans per subject.

The data were preprocessed and analyzed with statistical parametric mapping SPM99 (<http://www.fil.ion.ucl.ac.uk/spm/>). Prior to statistical analysis, all $T_2^*$ volumes were slice corrected, realigned to the first image in their respective run, transformed into a standard space, and then spatially smoothed with a 7-mm (FWHM) isotropic Gaussian kernel. The resulting data were then convolved with a hemodynamic response function plus a temporal derivative, proportionally scaled and filtered.
with a discrete cosine basis set (108-s cutoff period). Areas of significant brain activity were determined using linear contrasts. The resulting set of voxel values for each contrast constituted a statistical parametric map of the \( t \) statistic (SPM\(|t|) thresholded at \( p = .001 \) (uncorrected).

**Results**

**AB and PRP minus control.** Significant activations were found in the left postcentral (BA 3/1/2) and precentral (BA 4) gyri and extended down across the left middle (BA 6) and inferior frontal gyri (BA 44). Additional activity was noted in the left cingulate (BA 24) and medial frontal (BA 6/8) gyri (Fig. 1).

600-ms delay minus 200-ms delay. Significant activations were seen in the left superior (BA 6/8/10), middle (BA 9), and right inferior frontal gyri (BA 47). Significant activity was also detected bilaterally in the inferior parietal lobule (BA 39/40) and in the left putamen and thalamus (dorsal medial) (Fig. 1).

200-ms minus 600-ms delay. There were no significant activations produced by this comparison.

**PRP minus AB.** There was a significant activation of the right middle frontal gyrus (BA 8/9) extending ventrally into the medial frontal gyrus (BA 10). Smaller, but similar, loci of activation were also noted on the left side (Fig. 1).

**AB minus PRP.** There were no significant activations produced by this comparison.

**Discussion**

The results show that overlapping identification of two targets activate common regions in both AB and PRP tasks, including the left perirolandic, lateral premotor, and anterior cingulate regions. This activation appears to be linked to the motor and the attentional aspects inherent to both phenomena. A comparison of the activity observed within the short and long delays revealed greater activation in prefrontal and premotor regions during the longer delays across both tasks. These delay effects may be interpreted as a loss of processing efficiency seen at the shorter delays. This
outcome may appear counterintuitive at first because the prefrontal regions have long been thought to be implicated in task conditions in which heavy demands are made on the attentional processes (Passingham, 1996). One would assume that as task difficulty increased, so would the activity of attentional networks necessary to keep behavioral performance at a satisfactory level. This should be reflected by increased activity in the frontal regions. However, if task difficulty proceeds to a point where performance deteriorates, the decreased efficiency in processing should be reflected in reorganizations in attentional networks including decrements in activity, as illustrated in the reduced prefrontal activity obtained here. Finally, when compared to the AB effect, the PRP effect generated increased bilateral activations in the medial prefrontal region. The task differences observed suggest that the medial prefrontal activity may be linked to the added masking interference of the AB effect.

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24. The Versatile Frontal Lobes: A Metaanalysis of 1000 PET and fMRI Activations

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The distribution of frontal-lobe activations from PET/fMRI studies of perceptual/cognitive processes was analyzed. Findings that left and right frontal lobes were asymmetrically activated during verbal/nonverbal processing, and dorsal frontal cortex preferentially activated during spatial processing, provided evidence for material specificity. Evidence for process specificity was provided by findings that activation of distinct frontal areas was associated with specific processes, including (i) cingulate activation with executive attention, (ii) orbital activation with emotional perception and problem solving, (iii) right polar and ventral activation with episodic retrieval, (iv) dorsal activation with attention and working memory, and (v) left ventral activation with semantic processing. These results support, and sharpen, the notion of heterogeneity of frontal-lobe function.

In the present study a database of 1000 frontal-lobe activations from PET and fMRI studies of perceptual and cognitive processes (Cabeza & Nyberg, 2000) was used to address hypotheses about frontal-lobe function. The activations were located in medial frontal/cingulate cortex (N = 121), right lateral (N = 395), or left lateral (N = 484) frontal cortex and defined by x (lateral/medial), y (anterior/posterior), and z (superior/inferior) Talairach coordinates.
Lateralization of Activations during Processing of Verbal/Nonverbal Information

The first analysis examined the right lateral/left lateral distribution of activations from studies involving processing of verbal ($N = 341$) versus nonverbal ($N = 211$) information (the remaining 448 activations were not possible to categorize in a clean manner). The verbal category included studies of written and spoken language processing, verbal/numeric working memory, verbal episodic encoding and retrieval, semantic memory, and perceptual and conceptual priming. The nonverbal category included studies on face/space/smell perception, imagery of space/motion, episodic encoding and retrieval of objects/faces/locations, object/spatial working memory, and perceptual priming. It was found that left frontal activation was about twice as common than right frontal activation for verbal material (left/right distribution 201/98). For nonverbal materials, right frontal activation was slightly more frequent than left frontal activation (left/right distribution 88/101).

Superior/Inferior Distribution of Activations during Processing of Spatial/Nonspatial Information

The second analysis examined the location of activations along the dorsal/ventral ($z$) axis from studies involving processing of spatial ($N = 138$) versus nonspatial ($N = 862$) information. The spatial category included studies on orientation of attention, perception and imagery of space/motion, spatial working memory, and episodic encoding of spatial location. Whereas activations from studies involving nonspatial processing were evenly distributed above/below a $z$ value of 25, about twice as many activations from the spatial category fell above than below this divider (superior/inferior distribution 91/47).

Frequency of Medial Frontal (Cingulate) Activations under High/Low Demands on Executive Attention

The third analysis explored the frequency of activations in the anterior cingulate cortex under conditions of higher/lower demands on attentional control. The high demands category ($N = 89$) included studies on attention (variants of the Stroop task) and semantic memory (various generation tasks). The low demands category ($N = 44$) did also include studies on attention (sustained) and semantic memory (categorization), although the tasks in these studies did not put as strong demands on resolution of response conflicts and on response monitoring. It was found that the proportion of anterior cingulate activations in the high category ($N = 18$ or 20%) far exceeded that in the low category ($N = 3$ or 7%).

Distribution of Process-Specific Activations across Subregions of the Frontal Lobes

In the fourth and final analysis, the frontal lobes were divided into four subregions (Fig. 1), and the distribution of process-specific activations across these subregions was examined. The main results of this analysis are summarized in Fig. 1.

- In left ventral cortex ($N = 137$ activations), consistently activated processes included semantic memory (generation, $N = 36$), verbal/numeric working memory ($N = 13$), and verbal episodic encoding ($N = 13$). Right ventral cortex ($N = 76$) was associated with verbal episodic retrieval ($N = 11$), nonverbal episodic retrieval ($N = 8$), and episodic retrieval mode ($N = 10$).
- In right polar cortex ($N = 65$), a similar pattern as for right ventral cortex was
seen, including verbal episodic retrieval ($N = 9$), episodic retrieval success ($N = 11$), and episodic retrieval mode ($N = 9$). Left polar cortex ($N = 55$) was frequently activated during verbal/numeric working memory ($N = 6$).

- **Left dorsal cortex** ($N = 100$) was consistently activated during verbal/numeric ($N = 16$) and spatial ($N = 9$) working memory and during semantic memory (generation, $N = 8$). Right dorsal cortex ($N = 102$) was frequently activated for verbal/numeric ($N = 13$) and spatial ($N = 9$) working memory, verbal ($N = 15$) and nonverbal ($N = 9$) episodic retrieval, and attention (sustained and selective, $N = 8$).

- **Orbitofrontal** activations were scarce (left 27; right 22). Therefore, to increase the chance of finding consistent process-specific activations, left and right orbital activations ($N = 49$) were considered together. Orbital cortex was found to be activated during complex working memory operations (problem solving, $N = 5$) and during the perception of facial expressions ($N = 4$).

**Conclusions**

In the present study, we used a large database (1000 frontal activations) to examine the support for material-specific frontal activity. With the caveat that the number of activations for different processes differed widely, we also used the database to search for consistent process-specific activations in subregions of the frontal lobes. Below, we discuss the findings from these two sets of analyses:

**Material-specific activation of frontal cortex.**

- The left and right frontal lobes were asymmetrically involved in processing of verbal and nonverbal information. This is in agreement with similar suggestions based on neuropsychological studies (e.g., Milner, 1971). Left frontal activation was about twice as common than right frontal activation during processing of verbal information. The asymmetry was less pronounced for processing of nonverbal information, perhaps due to the possibility to verbally recode such information, but there was nevertheless a tendency for right lateralization of activations during nonverbal processing.

- The dorsal and ventral frontal cortices were differentially involved in processing of spatial information. An association between dorsal frontal areas and spatial
working memory has been proposed, although the support from functional neuroimaging for this proposal has been mixed (see Cabeza & Nyberg, 2000). In addition to spatial working memory, the present analysis was based on data from studies on orientation of attention, perception and imagery of space/motion, and encoding of spatial location. Hence, these results indicate that dorsal frontal areas are generally involved in spatial processing (cf. Goldman-Rakic et al., 1999).

**Process-specific activation of frontal cortex.**

- Increased executive demands were found to be associated with more frequent activation of the anterior cingulate cortex. This provides support for the idea that the anterior cingulate cortex is a central component of an attentional network (Posner & Petersen, 1990).
- Left ventral frontal cortex was frequently activated during semantic memory, verbal/numeric working memory, and verbal episodic encoding. This pattern suggests that this frontal area is engaged by tasks that involve ‘active processing of semantic information.’
- Right ventral and right polar frontal cortex were consistently activated by episodic retrieval processes. This is in line with the suggestion that these frontal areas are involved in mediating ‘episodic retrieval mode’ (see Cabeza & Nyberg, 2000).
- Bilateral dorsal frontal cortex was activated by verbal/numeric as well as spatial working memory tasks. This indicates that dorsal frontal cortex subserves ‘amodal working memory operations,’ which is in line with proposals that areas 9/46 are generally activated for tasks that require manipulation of the content of working memory (for discussion, see Cabeza & Nyberg, 2000).
- In addition to an involvement in working memory, right dorsal frontal cortex was consistently activated during verbal and nonverbal episodic retrieval and during sustained and selective attention. This pattern suggests a role of this frontal area in maintaining ‘focal attention’ on present and past events.
- Orbital frontal cortex was associated with perception of facial expression (anger, fear, disgust). There exist strong links between ventromedial frontal cortex and limbic structures and processing of different kinds of emotions seem to converge in area 47 (see Cabeza & Nyberg, 2000). Orbitofrontal cortex was also associated with problem-solving activity, including tests of Wisconsin card sorting and Tower of London. This is consistent with recent findings (Anderson et al., 1999) that patients with early frontal damage, involving the orbital area, perform poorly on such test (Wisconsin card sorting, Tower of Hanoi).

In conclusion, functional brain imaging studies have demonstrated involvement of the frontal lobes in a variety of mental operations, including attention, perception, imagery, language, and memory (Cabeza & Nyberg, 2000). The present analyses provide additional information on the functional role of the frontal lobes by revealing material-specific activation patterns as well as process-specific activation of subregions of the frontal lobes.

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Activation of lateral frontal cortices during memory tasks has been widely reported in functional neuroimaging studies using positron emission tomography (PET). These studies implicated that the frontal cortices had a certain role in human memory activities. In the present study we propose an anatomical–functional model of the frontal lobes in auditory verbal memory based on a review of PET activation studies of our own and others. The model, to which we referred as “the Sylvian fissure-centered model,” insists that the lateral frontal cortices, especially in the left hemisphere, are functionally segregated according to the distance from the Sylvian fissure. We speculate that the model reflects one possible aspect how the function of the frontal lobe is organized in processing verbal memories.

In recent years, relationship between human frontal lobes and memory processes has been increasingly discussed based on the results from activation paradigm with neuroimaging methodology. Activities of the frontal cortices observed with positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) have strongly suggested a possibility that human frontal cortices have a certain role in memory activities. So far the various but robust activations in the frontal lobes observed during memory tasks have been interpreted in terms of hemispheric asymmetry and functional segregation within the frontal lobe (see Desgranges et al., 1998, for a review). In the present study, we would like to propose a possible functional segregation of human lateral frontal cortices related to storage and recognition of verbal materials by reviewing several PET activation studies.

Materials and Methods

We reviewed total of eight PET activation studies on verbal memory. Three of them were studies of our own, two of which were studies concerning recognition of words from long-term memory (Fujii et al., 1997; Motooka et al., 1998) and the other was concerning storage of words in the long-term memory (Okuda et al., 2000). The other five deals with verbal short-term memory (Fiez et al., 1996, etc., all of which are referred to in Okuda et al., 2000).

Subjects were right-handed normal volunteers in all studies. Stimuli used were auditorily presented words (Fujii et al., 1997; Motooka et al., 1998; Okuda et al., 2000), visually presented words (Fiez et al., 1996), and visually presented letters (other four studies). In two recognition studies (Fujii et al., 1997; Motooka et al., 1998) subjects were required to repeat words that matched previously memorized words (delayed matching to sample task) as experimental tasks and simple oral expression task as a control. In the study on long-term storage (Okuda et al., 2000)
subjects were required to hold 10 words during another word repetition task in an experimental condition and only to perform the repetition task in a control condition. In studies on short-term memory subjects were required to phonologically maintain word pairs (Fiez et al., 1996) or letters (other four studies) in experimental tasks and performed a simple fixation task (Fiez et al., 1996) or visual matching tasks (other four studies) as a control.

We classified these eight data into three groups based on the stages of verbal memory, i.e., passive retrieval from the long-term store (recognition), long-term storage, and phonological maintenance in the short-term store. We plotted peak activation foci observed in lateral frontal cortices in each group onto one schematic brain surface sagittally oriented in Talairach space.

Results

The activation foci corresponding to each memory stage are plotted in Fig. 1. Interestingly, activation foci clustered in separate areas of the lateral frontal cortices according to the three memory stages. Two aspects seemed to characterize the arrangement of the clusters, i.e., hemispheric difference and segregation according to the distance from the Sylvian fissure.

At first, predominance in the left hemisphere for the stages of short-term maintenance and long-term storage are obvious, while activation foci exist similarly in bilateral hemispheres for the stage of recognition.

Second, especially in the left hemisphere, the activated foci seemed to cluster according to the distance from the Sylvian fissure. The cluster for the short-term mainte-
nance mainly occupied the central area adjacent to the Sylvian fissure in the posterior inferior frontal gyrus around Broca’s area and inferior portion of the precentral gyrus, although a couple of activation foci at the middle frontal gyrus also appeared. The activated foci for the long-term storage situated at more anterior part of the inferior frontal gyrus and the middle frontal gyrus surrounding the cluster for the short-term maintenance. The clusters for the recognition stage further surrounded the foci corresponding to the long-term storage. Therefore, they occupied the farthest area to the Sylvian fissure including the most anterior part of the inferior frontal gyrus, the middle and the superior frontal gyrus.

Discussion

Based on these data we propose an anatomical–functional model of storage/recognition of verbal materials in the frontal lobes in terms of the distance from the Sylvian fissure. This “Sylvian fissure-centered model” insists that the frontal lobes be functionally segregated in the concentric fashion.

In this model it is suggested that the core area adjacent to the Sylvian fissure subserves the verbal short-term memory. This area including Broca’s area has been argued to have an important role in subvocal rehearsal of verbal materials or inner speech (Fiez et al., 1996). Another cluster in the middle frontal area for the short-term maintenance stage may not be involved with verbal short-term memory per se; rather it may be related to certain cognitive components relevant to working memory as pointed out by Fiez et al. The area corresponding to the long-term storage may be related to hypothetical transitional phase between short-term and long-term memory (Okuda et al., 2000), which is situated in the intervening area between the area for short-term maintenance and that for recognition based on long-term memory. The last area, which occupies the farthest area to the Sylvian fissure, has a critical role in evaluating verbal materials in reference to memory information, rather than a role in phonological handling of verbal materials. The results that the area is represented bilaterally while the other two areas showed predominance in the left hemisphere support this idea. The area far from the Sylvian fissure might be less demanding for phonological activity and more demanding for cognitive operations apart from phonology.

The model we proposed might reflect a way of functioning of the frontal cortices both in verbal activities and memory processes. These data suggest that the way the frontal lobe contributes to verbal memory is highly complex. We intend to further evaluate this tentative hypothesis by future studies.

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26. Neural Mechanisms of Age-Related Changes in Human Working Memory

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We used event-related fMRI to investigate age-related differences in PFC activity during separate WM task components (encoding, maintenance, retrieval) with varying memory loads of verbal information. Younger adults showed greater PFC activity than older adults only in dorsolateral PFC, only during memory retrieval. Faster young subjects showed less dorsolateral PFC activation during retrieval than slower young subjects whereas the opposite pattern was observed in older adults. This result was replicated in two additional experiments using verbal and spatial information. Age-related changes in the dorsolateral PFC regions involved in memory retrieval may mediate declines in WM performance. These results suggest a relationship between neural activation and performance that is sigmoid in nature. Age-related differences in performance may be mediated by bias shifts in this sigmoid function.

Age-associated prefrontal cortex (PFC) decline has been documented in anatomical and physiological studies of human (e.g., Raz et al., 1997) and infrahuman primate brains. Age-associated differences in WM performance may be related to the PFC changes that occur with age. Neuroimaging studies suggest that PFC is functionally divided such that subcapacity (i.e., two to three items) maintenance of information (which is not generally affected by aging; e.g., Craik & Jennings, 1992) is supported by ventrolateral PFC regions. Dorsolateral PFC regions are engaged selectively in WM tasks that require supracapacity information maintenance (Rypma et al., 1999) or manipulation of the maintained information, tasks in which age-related performance differences are often observed.

Behavioral studies demonstrating age differences in WM maintenance when memory loads exceed capacity, and neurophysiological and neuroimaging studies demonstrating functional PFC subdivisions, have led us to hypothesize that the neural basis of age-related WM performance declines may be related specifically to age-related changes in dorsolateral, but not ventrolateral, PFC. We tested this hypothesis in three experiments using event-related functional MRI (fMRI). This method permitted us to examine age-related changes in neural activation patterns in dorsolateral and ventrolateral PFC uniquely associated with stimulus encoding, memory maintenance, and memory retrieval during these three WM tasks.

Method

Subjects. Younger subjects (M age = 25.0 years across experiments) were recruited from the University of Pennsylvania campus. Older subjects (M age = 68.8 years across experiments) were recruited from the Philadelphia area by newspaper ads. All subjects were screened for medical, neurological, or psychiatric illness.

Experiments 1 and 2. On each trial, subjects first encoded either two or six letters for 4 s, second retained them across an unfilled 12-s interval, and third determined, within 2 s, whether or not that letter was part of the memory set. A 16-s intertrial interval (ITI) followed each trial. Subjects responded by button press. In the scanner, each subject performed 10 blocks of eight trials.

Experiment 3. On each trial, an initial cue instructed subjects to attend to objects, locations, or both. Next, three objects appeared sequentially, for 1 s each, in different locations in a 3 × 3 grid, followed by an 8-s retention interval. A test probe then appeared for 2 s and then a 12-s ITI. On object trials, the test probe was an object
in the center of a grid; subjects responded “yes” if the probe corresponded to a studied item on that trial. On location trials, the test probe was a black dot in one grid cell and participants responded “yes” if it appeared in a location that an object had occupied on that trial. On combination trials, an object appeared in one grid cell and subjects responded “yes” if the test probe corresponded to a studied object/location pairing.

Image acquisition. Imaging was carried out on a 1.5-T GE Signa scanner with fast-gradient echoplanar imaging and a radiofrequency head coil. For each subject, sagittal and axial T1-weighted images were first obtained. During functional scanning, BOLD signal was obtained using a gradient echo, echoplanar sequence (TR = 2000 ms, TE = 50 ms). Resolution was 3.75 mm² in plane and 5 mm between planes (21 axial slices).

Data analysis. We modeled fMRI signal changes occurring during each task period with covariates composed of shifted BOLD impulse response functions. Relationships with each task period and the ITI were assessed by contrasts (yielding \( t \) statistics with \( \sim 1195 \) df) involving the parameter estimates that corresponded to the independent variable modeling each task period. Age-related activation differences in dorsolateral and ventrolateral PFC regions were assessed with random-effects tests of age differences in mean parameter estimates.

Results

Behavioral data. Performance data from Experiment 1 indicated that subjects performed the WM task with high accuracy. There were minimal accuracy differences between the two memory load conditions \( [F(1, 10) = 1.46, p < .25, Mse = 25.7] \). Reaction times (RT) were slower in the six-letter than in the two-letter condition \( [F(1, 10) = 29.0, p < .001] \). Accuracy rates were not significantly different between younger and older subjects \( (M \) younger = 89.6; \( M \) Older = 84.0; \( F(1, 10) = 1.24, p < .29) \) but younger subjects’ RTs were faster than older subjects’ RTs \( (M \) younger = 965.6 ms; \( M \) older = 1169.7; \( F(1,10) = 7.44, p < .02) \). Similar behavioral results were observed in the two replication experiments.

FMRI data. Analyses of imaging data in Experiment 1 revealed no significant age-related differences in ventrolateral PFC activation in either of the memory load conditions during any of the task periods (i.e., stimulus encoding, maintenance, and retrieval). In dorsolateral PFC, there were no significant age-related activation differences in dorsolateral and ventrolateral PFC regions during the encoding period and the retention period. Younger subjects did show significantly greater activation than older subjects in the six-letter condition, during the response period in dorsal PFC \( (M \) younger = 0.21, \( M \) older = 0.06; Mann–Whitney U, \( p = .01) \) but not ventral PFC \( (M \) younger = 0.13, \( M \) older = 0.09). No other effects approached significance (all \( ps > .10) \).

Subjects’ individual activation patterns suggested a possible relationship between dorsolateral PFC activity in the response period and RT. To test relationships between cortical activity and performance, we performed regression analyses of subjects’ overall RT and PFC activity. Tests of the regression coefficients that characterize the relationship between mean RT and ventrolateral PFC activity were nonsignificant in all task periods. In dorsolateral PFC in younger subjects, retrieval period regression coefficients showed a significant positive correlation between mean RT and cortical activity (slope = .84, \( p < .03) \) that accounted for 71% of the variance. In contrast, in dorsolateral PFC in older subjects, response period regression coefficients showed a significant negative correlation between mean RT and cortical activity (slope = −.85, \( p < .03) \) that accounted for 72% of the variance. These relationships are presented in Fig. 1.
FIG. 1. Scatterplots of normalized mean parameter estimates during retrieval in dorsolateral PFC versus RTs in younger (black squares, Experiment 1, slope = .84, \(r^2 = .71\), \(p < .03\); Experiment 2, slope = .87, \(r^2 = .76\), \(p < .01\); Experiment 3, slope = .85, \(r^2 = .72\), \(p < .03\); Experiment 2, slope = −.82, \(r^2 = .68\), \(p < .04\); Experiment 3, −.87, \(r^2 = .76\), \(p < .03\)).

Experiment 2 was conducted with a second group of younger and older subjects on the same WM task as Experiment 1 to determine the replicability of these findings. Experiment 3 was conducted with a third group of younger and older subjects and a different WM task to determine the generalizability of our findings. In both experiments, we observed similar activation patterns in dorsolateral PFC and ventrolateral PFC (see Fig. 1). In Experiment 2, response period regression coefficients in dorsolateral PFC showed a significant positive correlation between mean RT and cortical activity in younger subjects but a significant negative correlation between mean RT and cortical activity in older subjects (Fig. 1). No such correlations were observed in ventrolateral PFC. In Experiment 3 we also observed significant patterns of RT-fMRI signal correlations only in dorsolateral PFC that were positive for the younger age group but negative for the older age group. No such correlations were observed in ventrolateral PFC.

Discussion

We observed significant age-related differences in fMRI signal in dorsolateral PFC only during retrieval of high memory loads but minimal age-associated differences in ventrolateral PFC. Regression analyses indicated significant correlations between RT performance and PFC activity only in dorsolateral PFC, only during the response period. Slower young adults showed increased cortical activity relative to their faster counterparts, whereas slower older adults showed decreased cortical activity relative to their faster counterparts. These effects were also observed in (1) a second subject group performing the same WM task and (2) a third subject group performing a different WM task.

These results suggest that decreased speed of information retrieval at response (possibly reflecting less efficient memory-scanning processes) is related to increases in dorsolateral PFC activation for younger subjects, but to decreases in dorsolateral PFC activation for older subjects. The current results are consistent with processing-efficiency models based on behavioral research (Salthouse, 1996) and suggest one possible model for the neural correlates of reduced processing efficiency.

The age-related differences we observed in the relationship between neural activation...
and performance is consistent with response-selection models in which the probability of a given response is determined by the relative signal strength associated with each possible response. In this sigmoid function, middle ranges of neural activation result in large differences in signal and easy discrimination between potential responses. As neural activation levels move above or below this range, potential responses become progressively less discriminable (Cohen & Servan-Schreiber, 1992).

With aging, higher neural activation levels may be required for optimal response discriminability. That is to say, for older adults, the sigmoid activation function may be bias shifted. In this model, low activation levels lead to optimum response discriminability for younger adults but to suboptimum response discriminability for older adults. As neural activation levels increase and move rightward on the sigmoid function, response discriminability moves into the optimum range for older adults but into a supraoptimal range for younger adults. Thus, increases in neural activation will lead to improvements in performance for older adults but to decrements in performance for younger adults. Just such relationships between neural activation and performance were observed in the current data.

These results suggest, first, that distinct neural systems in dorsolateral and ventrolateral PFC selectively mediate different WM operations. Second, age-related WM decline may be tied more to age-related physiological changes in dorsolateral than in ventrolateral PFC during memory retrieval. Finally, age-related WM performance declines may be mediated by reductions in retrieval-related neural activity in dorsolateral PFC that adversely affect discrimination between potential responses.

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27. Prefrontal Systems Underlying Spontaneous and Directed Strategic Processing during Verbal Learning

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Prefrontal cortex supports strategic memory processes, including the ability to use semantic organizational strategies in novel or ambiguous learning situations. We used PET and a verbal learning paradigm to evaluate neural systems supporting spontaneous and directed use of semantic organizational strategies. There were three encoding conditions (Spontaneous, Di-
rected, Unrelated) and behavioral measures of semantic clustering. In graded PET contrasts (D > S > U), two activations were found in left inferior prefrontal cortex (IPFC) and left dorsolateral prefrontal cortex (DLPFC). Covariate analyses indicated that blood flow in orbitofrontal cortex (OFC) was strongly correlated with spontaneous use of semantic clustering strategies during free recall. Findings indicate that OFC plays an important, and previously unappreciated, role in strategic memory by supporting early mobilization of behavioral strategies in novel or ambiguous situations.

The prefrontal cortex (PFC) is implicated in episodic memory, especially in strategic aspects of encoding and retrieval that are closely tied to executive functioning. One example is semantic organization, whereby memory for word lists is enhanced by processing semantic relationships between items and reorganizing them into category groups. Patients with PFC lesions are less likely to use semantic organizational strategies than normal subjects (Gershberg & Shimamura, 1995).

There is also evidence that problems in PFC lesion groups are most likely to emerge in novel situations that lack external structure. For example, memory impairment is most apparent during free recall, and it improves disproportionately when subjects are provided with cues or instructions to use specific strategies (Gershberg & Shimamura, 1995). These observations indicate that one important function of PFC is to mobilize the effective use of behavioral strategies in ambiguous unstructured situations. Many patients may be able to use semantic organizational strategies when given explicit guidance yet fail to do so spontaneously.

Functional neuroimaging studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) indicate that specific territories of PFC contribute to different aspects of executive functioning. For example, semantic processing is supported by regions in left inferior PFC (IPFC; Demb et al., 1995), whereas the ability to update and manipulate items in working memory relies on dorsolateral PFC (DLPFC; D’Esposito et al., 1998). These executive function operations likely underlie verbal semantic organization.

Fletcher and colleagues (1998) used PET to study semantic organization. Their paradigm manipulated organizational difficulty across three related word lists with explicit instructions to utilize strategies. They found that one region of left DLPFC showed increased blood flow when the most difficult organization condition was compared to the two less demanding conditions. They did not find changes in left IPFC, a region previously implicated in semantic processing (Demb et al., 1995). One possible explanation for this is that all three encoding conditions used related word lists; thus, subjects were encouraged to process semantic relationships across all conditions.

The goal of the present study was to utilize PET to identify the neural basis of spontaneous and directed use of semantic organizational strategies during verbal learning. The design allowed us to manipulate levels of semantic clustering over three encoding conditions, including an unrelated list condition. More critically, we were able to determine patterns of brain activity that predicted the spontaneous application of effective strategies in ambiguous learning situations.

Methods

Subjects. Eight normal right-handed adults (four males, four females), with a mean age of 28 years, participated in this study. All were free of neurologic and psychiatric illness and medication free.

Experimental paradigm. Our paradigm was modeled closely after the California Verbal Learning Test (CVLT), a well-characterized measure of strategic verbal memory. Our word lists were generated from 32 categories of words, with six words in
each category. During each encoding condition, participants heard 24 words. In the two related-list conditions, items were presented so that no two words from the same category occurred consecutively.

Participants underwent eight scans across four conditions. The conditions were: (1) **Spontaneous**—related words in four semantic categories (6 words each) and subjects were not instructed about this organization beforehand nor given any practice with related lists; (2) **Directed**—related words in four semantic categories (6 words each) and subjects were explicitly instructed to notice the four categories and use them to improve their memory (they were not told the category names); (3) **Unrelated**—words in the list did not share obvious semantic relationships; and (4) **Fixation Baseline**—participants were instructed to look at the center fixation cross and rest.

Behavioral measures were collected after each scan: Free recall, Cued recall, Recognition, and Semantic clustering. For semantic clustering, “cluster” was defined as consecutive recall of two words from the same category during free recall. The Semantic clustering score was calculated as: \[ \text{clusters/(words recalled - categories recalled)} \].

**PET scanning.** PET facilities and procedures are previously described. PET data were acquired in eight 60-s scans while subjects performed the cognitive tasks and inhaled \(^{15}\)O-labeled CO\(_2\) gas. Each scan was followed by a 10-min washout period. PET images were motion corrected and transformed to Talairach space. Images were smoothed and statistical analyses were performed using SPM96 (Wellcome Department of Cognitive Neurology, London, UK). Images were normalized to 50 ml/min per 100 g. For the graded analyses, PET data were analyzed using ANOVA and the general linear model, with Condition as an explanatory variable and the two scans for each condition entered as replicates. For the covariate analyses, the semantic clustering score was regressed onto PET blood flow data for that condition using the Covariates Only module. Activations were thresholded at \(z > 3.09\).

**Results**

Behavioral results are summarized in Table 1, Part A. ANOVA indicated that subjects obtained higher semantic clustering scores in the Directed condition than in the Spontaneous condition. During the Spontaneous condition, we noted that subjects initiated a strategy (either semantic clustering or serial order) early in the course of the first learning trial and continued with it through the second (ANOVA confirmed the absence of Scan 1/Scan 2 effects for clustering). Subjects who did not spontaneously cluster did so at very high levels in the Directed condition.

The primary PET results are summarized in Table 1, Part B. We performed additional direct contrasts between each of the conditions which are not discussed here for space limitations. The graded contrast was defined (weighted) such that activations represented voxels where blood flow increased in a graded fashion (Directed > Spontaneous > Unrelated). This analysis identified two (and only two) regions of significant activation (Table 1): (1) Left DLPFC (BA 9) and (2) Left IPFC (~BA 45/46). The two regions of left PFC identified in this study were predicted \(a\ priori\) based on previous studies. The left DLPFC activation corresponds to BA 9 and is exactly the same territory identified by Fletcher and colleagues (1998). The left IPFC activation corresponds to BA 45/46 and is within a region identified in numerous other investigations of verbal semantic processing (Demb et al., 1995).

Covariate analyses were performed between PET blood flow measures during encoding and the Semantic clustering scores measured during immediate Free recall (see Table 1). Activations identified in this way can be conceptualized as defining regions in which blood flow levels measured during encoding predicted subsequent
TABLE 1

A. Summary of Behavioral Performance Data (Standard Deviations in Parentheses)

<table>
<thead>
<tr>
<th></th>
<th>Spontaneous</th>
<th>Directed</th>
<th>Unrelated</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semantic clustering</td>
<td>.71 (.25)</td>
<td>.87 (.16)</td>
<td>N/A</td>
<td>D &gt; S</td>
</tr>
<tr>
<td>Free recall</td>
<td>16.31 (3.32)</td>
<td>17.81 (2.75)</td>
<td>14.00 (6.16)</td>
<td>D &gt; U</td>
</tr>
<tr>
<td>Cued recall</td>
<td>20.25 (2.25)</td>
<td>20.00 (3.07)</td>
<td>N/A</td>
<td>n.s.</td>
</tr>
<tr>
<td>Recognition</td>
<td>.98 (.03)</td>
<td>.98 (.02)</td>
<td>.97 (.03)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

B. Summary of Primary PET Data

<table>
<thead>
<tr>
<th></th>
<th>Coordinates</th>
<th>Region (Brodman area)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graded contrast by clustering D &gt; S &gt; U</td>
<td>3.36</td>
<td>−36</td>
</tr>
<tr>
<td></td>
<td>3.20</td>
<td>−36</td>
</tr>
<tr>
<td>Covariate analyses with clustering Spontaneous 1</td>
<td>4.38</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>4.31</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>4.01</td>
<td>12</td>
</tr>
<tr>
<td>Spontaneous 2</td>
<td>3.67</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>3.43</td>
<td>−16</td>
</tr>
<tr>
<td>Directed 1</td>
<td>3.89</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>3.40</td>
<td>−50</td>
</tr>
<tr>
<td>Directed 2</td>
<td>none &gt;3.09</td>
<td></td>
</tr>
</tbody>
</table>

strategic behavior during recall. Analyses in the first Spontaneous scan identified an activations in right ventromedial prefrontal with the greatest spatial extent located in orbitofrontal cortex (OFC). Thus, subjects with higher blood flow in OFC during encoding were the ones who later spontaneously clustered during recall.

**Discussion**

This study identified three prefrontal regions that appear to make distinct contributions to strategic verbal memory. Two regions in left PFC varied in the graded analyses that were designed to parallel actual levels of semantic organization (Directed > Spontaneous > Unrelated). These were left DLPFC, corresponding to BA 9, and left IPFC, extending across the border of BA 45 and 46. The design of the study allows us to implicate these regions directly in the cognitive operations underlying semantic organization. The left DLPFC activation is identical to the one identified by Fletcher et al. (1998). Previous research indicates that this region plays a critical role in monitoring, updating, and reorganizing items in working memory (e.g., D’Esposito et al., 1998). Left IPFC has been previously implicated in semantic processing (e.g., Demb et al., 1995). Our results, combined with previous research, indicate that these two regions of left PFC perform critical operations in support of semantic organization.

The most unique aspect of our paradigm is that it enabled us to examine brain regions that support spontaneous mobilization of semantic organizational strategies. Covariate analyses indicated that blood flow in OFC was strongly correlated ($r = .95$ to $.97$) with spontaneous use of semantic clustering strategies during free recall. Thus, blood flow in OFC predicted which subjects would later exhibit effective semantic strategies. Results of these analyses strongly implicate OFC, especially right OFC, in early processes supporting the spontaneous mobilization of strategies in ambiguous learning situations. Our findings in OFC are consistent with previous animal and human lesion data, identifying OFC in decision making and strategy mobilization...
Our findings indicate that OFC plays an important, and previously unappreciated, role in strategic memory by supporting early mobilization of behavioral strategies in novel or ambiguous situations. These strategies, which include making semantic comparisons and updating and reorganizing items in working memory, are mediated in inferior and dorsal left PFC.

REFERENCES


28. Learning Serial Order of Interval, Spatial, and Object Information: An fMRI Study on Sequencing

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Brain activations elicited by the processing of sequential interval information (rhythms) were compared with those elicited by the processing of sequential spatial information (positions) and object information (abstract symbols) in a serial learning paradigm. Relative to a control condition, all tasks elicited brain activations in a corticosubcortical network including in supplementary motor area (SMA), premotor cortex (PMC), and frontal opercular cortex (BA 44), suggesting that these areas are involved generally during sequencing. However, direct comparisons between the three serial learning tasks revealed significantly higher activations in BA 44 and SMA for the rhythm task, in pre-SMA for the object task, and in the frontal eye fields (FEF) for the position task. We therefore suggest a common brain network that underlies the processing of sequential information, with subcomponents subserving different information specific requirements.

Introduction

The ability to learn, memorize, and anticipate the temporal structure of sequential perceptual input is a core prerequisite to be oriented and behave adequately in an environment shaped by continuously changing conditions. The large cortical belt of the premotor cortex (PMC), extending medially into the supplementary motor area (SMA) and laterally into the frontal opercular cortex (BA 44), is suggested to play an important role in sequence processing (Schubotz et al., 2000; Halsband et al., 1993). However, it remains an open question if different areas of this cortical network are specialized for different aspects of sequencing. Our study addressed the question if there are distinct modulations of frontal cortical activation when subjects are required to learn stimulus sequences of different informational domains: temporal inter-
vals, positions, or objects. Subjects were required to learn short sequences and to monitor several repetitions for deviants. A baseline condition controlled for perceptual and preparatory (attentional) effects.

**Method**

Twelve healthy right-handed subjects (8 male and 4 female, ages 19–27 years, mean age 24) participated in the study. Four tasks (Rhythm R, Position P, Object O, Control C) were presented visually in randomized order and announced by verbal cues. Each screen display showed two equal objects arranged on two opposite positions on a virtual circle. Within each trial, 12 of these pictures were shown successively. The first three pictures constituted the sequence to be memorized with regard to its temporal order (picture 1-2-3). The following 3 × 3 pictures were repetitions of this sequence, but only with regard to the task relevant informational dimension. In the $R$ ($P, O$) task, subjects had to attend only to the display durations (positions, objects) of the sequence and to indicate omissions (sequential deviants) of a duration (position, object) in subsequent repetitions, respectively (deviant probability .38). In the $C$ condition, subjects had to press the response button if the fixation sign changed in size out of turn, i.e., earlier or later than between the succeeding repetitions (picture 3/4, 6/7, or 9/10).

**Scanning Procedure**

Imaging was performed at 3 T on a Bruker Medspec 30/100 system equipped with the standard bird cage head coil. High-resolution whole brain images were acquired from each subject to improve the localization of activation foci using a T1-weighted three-dimensional segmented MDEFT sequence (128 sagittal slices, 1.5 mm thick, 265 × 265-pixel matrix). To align the echoplanar functional images to the three-dimensional images, a set of two-dimensional anatomical images in plane with the functional images were acquired for each subject immediately prior to the functional experiment, using an IR-RARE sequence (TE = 20 ms, TR = 3750 ms, 512 × 512-pixel matrix). Functional images were acquired using a single-shot gradient EPI sequence (TE = 40 ms, 64 × 64 pixel matrix, flip angle 40°, FOV = 192 mm) sensitive to BOLD contrast. During each trial eight images were obtained from 16 axial slices (5 mm thick, spacing 2 mm) at the rate of 2 s per image (16 slices). Slices were positioned parallel to the bicommissural plane (AC-PC), with one image covering the whole brain.

**Data analysis.** The fMRI data were processed using the software package LIPSIA (Lohmann et al., 1999). In the preprocessing, low-frequency signals were suppressed by applying a 1/120-Hz highpass filter (baseline correction). For the anatomical registration, anatomical slices geometrically aligned with the functional slices were used to compute a transformation matrix, containing rotational and translational parameters that registers the anatomical slices with the 3D reference T1 data set. Each individual transformation matrix was scaled to the standard brain size ($x = 135, y = 175, z = 120$ mm) by applying a linear scaling. Finally, these normalized transformation matrices were applied to the individual raw functional data. Slice gaps were scaled using a trilinear interpolation, generating output data with a spatial resolution of 3 mm³. The statistical analysis was based on a least squares estimation using the general linear model for serially autocorrelated observations. The design matrix was generated with a boxcar function model and a response delay of 6 s. The degrees of freedom were adjusted. The output images were $F$-thresholded at a probability of $p = .0001$ and profiled using a linear compound with the $t$ statistic.
To display and analyze the $p$ values from the $t$ statistics, $t$ values were then converted to $z$ scores, and $z$ scores were thresholded at $z = 8.0$, which corresponds to an $\alpha = 1.25 \times 10^{-15}$.

**Results**

In contrast to the baseline (task C), all conditions elicited activations within a cortical and subcortical network including the SMA, the PMC, the inferior frontal sulcus (IFS), and the inferior parietal sulcus (IPS). Direct comparisons between the serial learning tasks exposed significantly higher activations according to the specific contrast, as shown in Fig. 1. Thus, significantly higher activations during the interval task as compared to the other tasks ($R > O, P$) were found in SMA, BA 44, and in the basal ganglia (BG) (top panel). In contrast, higher activations during the position task ($P > O, R$) were significant in the frontal eye fields (FEF), the inferior lateral PMC (iPMC), the motion area (MT), the supramarginal gyrus (Gsm), and the mesial BA 7 (middle panel). Finally, the object task ($O > P, R$) led to higher activations in the pre-SMA, the IFS, the left superior PMC, the posterior IPS, and the fusiform gyrus (FG) (bottom panel).

**Discussion**

Since the present study focuses on frontal, especially on premotor, activation, data concerning the parietal lobe will be discussed elsewhere.

*SMA and pre-SMA.* Independent of the informational domain of the stimulus material, all serial learning (sequencing) tasks led to significant activations in the premotor area and its mesial as well as lateral anatomical extensions. In order to differentiate these similar activation patterns, direct comparisons between the three serial learning tasks ($R, P, O$) were computed. The interval (rhythm) task $R$ revealed
higher activation in the SMA, whereas the object task *O* elicited more pre-SMA activation. Both the SMA and the pre-SMA belong to the mesial part of the PMC that plays a major role in the preparation and processing of sequential movements, especially those that are internally guided and performed on the basis of memory (Halsband et al., 1993). The neurophysiological characteristics of the mesial PMC, as well as imaging studies, support the idea that the pre-SMA is involved in higher hierarchical or more complex roles in motor control than the SMA proper. Since the *O* task in our study was much more abstract than the *R* task, in the sense that we normally do not have to learn or memorize sequences of objects in our everyday life, this might be an explanation for the pre-SMA activation in the *O* task as opposed to the SMA activation in the *R* task.

**FEF.** In the *P* task, the FEFs were significantly more activated than in the other tasks. Lesion studies in monkeys have shown that both the covert detection and the overt orientation toward visual stimuli require intact FEFs. Accordingly, imaging studies indicate that areas involved in oculomotor execution are also recruited during oculomotor programming. Thus, a network of parietal and frontal cortical areas including the FEF mediates the covert shift and allocation of attention to visual locations. This is supported by the finding that voluntary as well as imagined saccades lead to a significant FEF activation. Moreover, the FEF is suggested to be involved in maintaining short-term mnemonic visuospatial representations (Zarahn et al., 1999). These findings provide an explanation for our data, since the visuospatial properties of the sequential stimulation could be ignored during the *R* and the *O* task, whereas they were the core information to be processed in the *P* task.

**Frontal opercular cortex (BA 44).** Activations in the frontal opercular cortex (BA 44) were significantly stronger for the *R* task than for the other tasks. The functions ascribed to the frontal opercular cortex (“Broca’s area”) although traditionally restricted to speech and language are today supplemented by nonlinguistic functions, as indicated by patient studies as well as imaging studies. BA 44 has been described as a multifunction organ adapted to the regulation of sequential activity in several different domains. Therefore, the activation of this area caused by the *R* task in the present study might reflect sequencing processes, i.e., the analysis of units of specific durations ordered in time. This is in accordance with the finding that Broca’s area is activated when subjects have to decide whether rhythms are isochronous or not or detect rhythmic deviants (Schubotz et al., 2000).

**REFERENCES**


29. Neural Correlates of Executive Processing in Perceptual-Motor Task Performance

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We manipulated two factors that differentially affect the duration of some of the processes involved in the performance of a perceptual-motor task. Participants performed a choice-reaction task during fMRI scanning under two difficulty levels for each factor. Behavioral results confirm the independent effects of these factors. Neuroimaging results associate stimulus-encoding processing with activity in prefrontal, premotor, and parietal cortices, which is distinct from the activity in prefrontal, premotor, and parietal cortices associated with response-selection processes. Little activation was found for the interaction of these two factors. These data are consistent with previous research and are among the first to show independent additive effects of factors in both behavioral and neuroimaging data.

One of the roles often ascribed to the PFC (specifically the dorsal PFC) is that of mediating so-called “executive” processes. Baddeley’s tripartite theory of working memory (WM; 1986) postulates that the PFC carries out processes that deploy capacity to subservient processes required to carry out memory, learning, or other mental processing. These executive processes, though often not clearly defined, usually refer to processes that attend to, control, initiate, monitor, and plan behavior.

Much of the evidence for these processes and their localization in the PFC comes from work with patients with frontal lesions. Damage to the PFC often produces deficits in a patient’s ability to plan and control behavior. Patients often have difficulty executing behaviors in a proper sequence, switching between competing rules and tasks, and remembering goals (McCarthy & Warrington, 1990). The use of patients to study executive control is one reason these processes often remain ill defined. The tasks and procedures traditionally used in neuropsychological research have often been too complicated to allow one to specify clearly the nature of executive processing. For example, one popular task is the Wisconsin Card Sorting Test (WCST). In the WCST, patients have a stack of cards with various shapes of different colors, numbers, and patterns. Participants must sort these cards by shape, number, color, or pattern. The sorting rule changes without the patients knowledge. The WCST is a very complicated task. It may involve executive processes that identify the stimuli, update memory for the current task rule, inhibit previous rules, select the appropriate response, and inhibit previous responses. Many patients with PFC lesions have difficulty performing this task. This suggests that the PFC is involved in one or more of these executive processes. However, because of the diffuse nature of the brain damage of many of the patients studied thus far, and its effects on cognitive processing, existing research with frontal patients does not allow one to dissociate the distinct executive subprocesses that are subserved by the PFC. Thus the extent of PFC involvement in any of one of these executive control processes remains unknown.

This study attempts to study some of the basic processes that underlie the performance of the WCST and other tasks using neuroimaging and simpler tasks, whose required mental processes are theoretically well formulated. Although some of these basic mental processes have been studied in previous neuroimaging experiments (e.g., Deiber et al., 1991), this is the first investigation of these processes whose investigative technique relies heavily on cognitive theory. Behavioral research suggests that stimulus-encoding and response-selection processes are serial discrete mental processes. Manipulation of some factors affect the duration of one stage but not the
other and vice versa (Sternberg, 1998). This neuroimaging study builds on this result to localize these processes as well as to test their independence using the neuroimaging signal.

Method

Participants performed a well-practiced choice-reaction task during fMRI scanning under two difficulty levels for each factor. On each trial of this experiment, participants are presented a row of four white open circles in the center of a black computer screen. After a foreperiod of 850 ms, one of the circles is filled in. Depending on the condition, participants make either a compatible or an incompatible response to the target circle. This manipulation has been shown to affect the duration of response selection (Sternberg, 1969). Additionally, on some trials, the target circle is filled in with white (high contrast) on other trials the target is filled in with gray (low contrast). This manipulation has been shown to affect the duration of stimulus encoding (Sternberg, 1998).

Participants practice these tasks for three sessions before being scanned. They then perform 12 fMRI scans of each task in separate blocks of 10 trials, which repeat three times throughout a scan. Each block lasts for 16 s, which has been shown to maximize signal in blocked designs (D’Esposito et al., 1999).

The fMRI comparisons of interest were for the main effect of contrast (i.e., between the two contrast conditions across the two levels of the mapping condition), the main effect of mapping (i.e., between the two mapping conditions across the two levels of the contrast condition), and for the interaction.

Results

Our behavioral results confirm the independent effects of these factors. The mean RTs for a representative participant were 420, 510, 584, and 692 ms for the high direct, low direct, high indirect, and low contrast indirect mapping blocks, respectively. Both main effects were reliable ($p < .0005$, in both cases). The interaction was not ($p > .35$). These data are consistent with previous behavioral research (Sternberg, 1998) and suggest that stimulus contrast affected the duration of stimulus encoding and stimulus-response compatibility affected the duration of response selection. Our neuroimaging results (Fig. 1) suggest that increased stimulus-encoding difficulty is associated with increased activity mostly in right prefrontal, premotor, and parietal cortices, whereas increased response selection difficulty is associated with increased activity mostly in left prefrontal, premotor, and bilateral parietal cortices. Little activation was found for the interaction of these two factors.

Conclusion

These data are consistent with previous research (D’Esposito et al., 1999; Deiber et al., 1991; McCarthy & Warrington, 1990). They suggest that stimulus encoding is mediated by a frontal–parietal network in this task, and that response selection is subserved by a different network involving frontal, premotor, and parietal areas. These results show that it is possible to find interpretable brain activation using very simple perceptual-motor tasks. By doing so we can begin to dissociate and localize the multiple control processes involved in the performance of more complicated tasks (e.g., WCST).

Additionally, these data are among the first to show independent additive effects of factors in both behavioral and neuroimaging data. The correspondences between
FIG. 1. fMRI activation from a representative participant. The top two images show two contiguous slices for the main effect of stimulus contrast. The bottom two images show the same two contiguous slices for the main effect of stimulus-response compatibility. The interaction image showed no coherent pattern of activation.

these two types of dependent measures (i.e., RT and fMRI signal) highlight the power of using cognitive theory to guide neuroimaging research.

REFERENCES


30. The Role of Medial Prefrontal Cortex in the Representation of Task-Specific Meaning

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Two positron emission tomography (PET) studies are presented which address the neural correlates of representations in different central executive tasks. A role is identified for left medial prefrontal cortex in the generation, representation, and choice between alternative response mappings for individual stimuli. This system is involved in central processing of sound structure, or read words, when the task requires that the stimuli be assessed in a novel and ambiguous manner, in which multiple candidate responses are considered. Activity in this
region correlates with longer reaction times in such choice tasks, but not in other tasks where
the response class is not ambiguous. © 2001 Academic Press

The modeling of central executive function has tended to focus on the cognitive
processes, with emphasis on potential elements such as planning, monitoring, and
the control of action (Shallice, 1988). Neuropsychological findings support these pro-
cessing distinctions in complex central executive tasks (Burgess, Veitch, Costello, &
Shallice, 2000). Other approaches to modeling central executive function have at-
ttempted to stress the role of task representation in executive function or its breakdown
(Barnard, 1998). Thus, a subject’s understanding of what they have been asked to
do will affect their response in a manner not necessarily explicitly specified in the
question (Scott, Barnard, & May, in press). In two neuroimaging studies we have
demonstrated potential neural correlates of such task-dependent representations.

In the first study subjects classified distorted speech sounds into speech-like and
not-speech-like categories. Although intended as a study of speech perception, there
was a significant effect of type of response on activity (regional cerebral blood flow)
in the left medial prefrontal cortex and dorsomedial thalamus. As subjects made more
‘not-speech-like’ responses, there was greater activity in these regions, which have
strong, reciprocal anatomical connections. The subjects took longer to make these
responses, and we interpreted this result as demonstrating the neural substrates of
generating and deciding between multiple possible sources for the distorted noises
when a nonspeech response was made.

We carried out a further study to investigate this hypothesis by visually presenting
subjects with nouns and asking them to perform two different tasks of similar dif-
culty but very different representational demands. Nine subjects performed tasks of
different representational content on the same sets of word stimuli and the regional
brain activity was measured with PET. The stimuli were disyllabic and trisyllabic
nouns, matched for concreteness, imageability, and frequency. Stimuli were pre-
sented for 750-ms duration on a computer screen, at a frequency of one per 2 s.
Subjects performed a semantic task (could the word apply to a human being or not)
or a structural task (did the word have three syllables or not) or ‘passively’ read the
words. Each condition was presented five times without repeating the stimuli. The
two choice conditions were chosen to stress different representational forms of the
same words. When the subjects made the ‘human’ decision, they had to consider
whether the word could have any semantic human role. For some words, such as
mother or baby, this is rapidly decided. For other words, such as candidate or subject,
there are two possible meanings, one of which has a direct human referent. Other
words, such as copper (UK slang for policeman) or honey (U.S. slang for significant
other) have even more ambiguity. The subjects had to consider each word in terms
of its applicability to human beings and then this extensively before categorizing it as
human. In contrast, the syllable task was to decide if a word had three syllables or
not. This strongly emphasized the representation of the sound form of a word. Once
the number of syllables had been counted, however, there was no further ambiguity
(three is not confusable with two or four). Thus, this task did not make significant
demands on a system responsible for the consideration of multiple possible responses.
Each word was presented once for passive reading, human judgments, and syllable
judgments. Any one word was presented for passive reading after it had been assessed
for humanness (to ensure that the semantic task was novel).

Behaviorally, there was no significant main effect of type of choice on reaction
times. However, there was a significant interaction: the subjects took longer to re-
respond ‘no’ in the human condition. This was consistent with their spending longer
ruling out the possibility the word could apply to a human being.
FIG. 1. Medial and lateral views of the left hemisphere, showing projections of the contrast of semantic choice with syllable choice. This revealed greater activity in the left medial prefrontal gyrus, left inferior frontal gyrus, left superior temporal sulcus and anterior temporal pole, and left angular gyrus.

The contrast of semantic choice with syllable choice revealed a distributed system, in which greater activity was seen in the left medial prefrontal gyrus (caudal to the cingulate gyrus), left inferior frontal gyrus, left superior temporal sulcus and anterior temporal pole, left parahippocampus, left angular gyrus, and dorsomedial thalamus (Fig. 1). Although his system has been identified in previous studies of semantic processing (Binder, Frost, Hammeke, Cox, Rao, & Prieto 1997) ours is the first to infer a specific role for the left medial prefrontal cortex. Consistent with our previous study, there was a positive correlation of reaction times with activation in left medial prefrontal cortex for semantic processing, but not for the syllable judgment tasks. This relationship was not seen in the inferior frontal gyrus or anterior temporal pole.

Regions that were more active for syllable counting included regions involved in controlling eye movements (posterior parietal cortex and frontal eye fields) made by the subjects as they scanned forward and back across each word while deciding its sound structure. There were additional, more anterior biparietal activations that we attribute to the act of counting. There was no relationship in these areas with reaction time.

In conclusion, we propose that the medial prefrontal cortex has a role in central executive tasks by supporting candidate representations of the stimulus currently under consideration. So far, using linguistic stimuli, we have shown the medial prefrontal response to be left lateralized. If there is ambiguity in the meaning, or the relationship to the possible responses, there is increased activity in this region. This processing load is heavy in semantic processing (not least because any one word can have several referents and any one semantic item in the world has many semantic features that can be considered). It is also used when a response label must be attached to a meaningless stimulus, such as distorted speech, in terms of the task instructions (did this sound come from a human being, or not?). When the task is semantic in nature, the coactivation of other regions in the left hemisphere indicates how this prefrontal activation relates to more posterior regions involved more directly in access to semantic knowledge.

REFERENCES


31. Contribution of the Left Prefrontal Cortex for Retrieval of Episodic Memory: A Functional MRI Study


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We examined the fMRI prefrontal activities associated with two forms of episodic retrieval, i.e., retrieval for which complex cognitive activities are required and one for which simple recognition is enough. The two types of retrieval activated overlapping and separate brain areas. The former included the bilateral parahippocampal, cerebellar hemispheres, medial and inferior occipital, and right prefrontal and left inferior temporal areas, while the left frontal area was activated only with the complex retrieval task. These findings suggest differential involvement of each prefrontal area for these two types of retrieval. The right prefrontal area is primarily related to simple or basic retrieval of episodic items such as a single word or picture, while the left to complex or systematic retrieval such as integration among episodic items.

The term episodic memory has been employed for a type of memory that is stored with temporal and spatial information attached. Many functional neuroimaging studies have reported activities of the right prefrontal cortex during retrieval of episodic memory (for review, Tulving et al., 1994). In most of these studies, memory processes investigated were episodic retrieval processes of a single item such as words or pictures.

Although these findings are important, human episodic memory must be far more complex as it contains many items. When we remember an episode in daily life, we retrieve not a single item but an array of items in an organized form.

The aim of the present study is to identify brain regions associated with retrieval of an organized content from fragmented cues.

**Materials and Methods**

**Participants**

Four healthy right-handed normal volunteers (four men; age range, 19–28 years) participated in the study. Informed consents were obtained from all participants based on the institutional guidelines. All procedures for this study received prior approval from the institutional human research review committee of the Electrotechnical Laboratory.

**Task Procedures**

*Encoding session.* We prepared 50 four-scene comic strips from a comic book for the present study [AIMUYACCHI (My name is Yacchi), © Copyright, Aska Gotoh, all rights reserved]. Each four-scene strip makes up a story. First, the subjects...
were requested to concentrate on a story by reading narrative portion of the strip and memorize the story by a self-determined pace.

Next the experimenter asked them to pay good attention to its pictorial portion. This session was started 1 h before scanning and was continued for about 30 min. Thus, the subjects had to retain these stimuli for about 30 min.

Retrieval session with MRI scanning. Each stimulus consisted of a pair of scenes chosen from the same comic book. Two scenes were arranged in vertical direction. Each stimulus was presented for 4 s without interval between stimuli. Stimuli were presented through a projector and back-projected to a screen placed beyond the subject’s feet in front of the scanner table. The subjects were able to see the screen through a mirror fixed into the head cage. In all tasks, a set of stimuli constituted with 10 targets and 10 distracters. The subjects were asked to push button 1 with the index finger when the targets appeared on the screen and to push button 2 with the middle finger when the distracters appeared.

The first task was a visual identification (VI) task, in which the subjects were required to judge whether they can identify at least one female character in the two scenes. All stimuli were novel with no memory required.

In the second task, the subjects were shown the first and last scenes from the strips, which had been presented before the scan. They were asked to judge whether these two scenes are from the same strip or not. They had to retrieve a whole story of a strip in order to succeed. We called this task as complex retrieval (CR) task.

In the third task, the subjects were shown two scenes and were asked to judge whether both of them belonged to the memorized strips or not. We called this simple retrieval (SR) task.

A sequential boxcar design was employed, in which three experimental tasks were alternated. In one run, the order of each block task was the following: VI, CR, SR, VI, CR, and SR. Thus, there were total 120 stimuli in one run. The subjects were required to participate in two runs, which were designed with the similar experimental procedures.

Scanning Methods and Data Analyses

All MRI studies were carried out by a 3-T GE Signa LX (General Electric, Milwau-kee, WI). The subjects were positioned in the scanner, and the head was immobilized with support cushions. A gradient echo EPI sequence modified by EPIBOLD sequence was used for functional imaging with the following parameters: TR = 4000 ms, TE = 32.3 ms, FOV = 20 × 20 cm², matrix sizes = 64 × 64, flip angle = 90°, slice thickness/gap = 8/2 mm. Twenty coronal slices were obtained, and 120 sequential images of each slice were collected in each run.

The analysis of the functional MRI data involved some steps using the software Statistical Parametric Mapping 96 (SPM96; Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 4 (Mathworks, Incorporated, Sherborn, MA). First, 120 sequential images acquired from each subject were realigned to the first image of those. Second, the realigned images from each subject were transformed and normalized into standard space (Talairach & Tournoux, 1988) using EPI template and smoothed using Gaussian kernel of FWHM of 10 mm. Third, the effects of tasks on signal intensity at each voxel were estimated using random effect model. The effects of each comparison were estimated using general linear model, which yielded t statistics (expressed as a Z score) for a given comparison at each voxel. The activation was considered significant if it had a cluster of voxel above Z > 3.09 (p < .001, corrected p < .05) with maximum Z value.
Results

Behavioral Data

The corrected response (i.e., hits–false alarm) scores were measured in three tasks. The one-way ANOVA for scores of each task showed the significant effect of task difference \[F(2, 9) = 10.07, p < .01\]. The post hoc analyses using LSD procedure detected the significant difference between VI (mean = 0.93, SD = 0.01) and SR (mean = 0.70, SD = 0.07) and CR (mean = 0.89, SD = 0.15) and SR.

Functional MRI Data

Activated areas with the complex retrieval task. To detect activated areas associated with the complex retrieval task, we compared the brain activities of CR with those of VI. In the right hemisphere, activated areas were observed in the middle frontal gyrus (BA 9/46), inferior frontal gyrus (BA 47), parahippocampal gyrus (BA 28), lingual gyrus (BA 18), inferior occipital gyrus (BA 18), medial occipital gyrus (BA 19), and cerebellar hemisphere. In the left hemisphere, we identified significant activities in the middle frontal gyrus (BA 9), middle temporal gyrus (BA 21), parahippocampal gyrus (BA 27), fusiform gyrus (BA 19/37), lingual gyrus, medial occipital gyrus, cerebellar hemisphere, and cerebellar vermis.

Activated areas with the simple retrieval task. We compared SR with VI to detect significantly activated areas associated with the simple retrieval task. This analysis showed significant activated areas of the middle frontal gyrus (BA 46), inferior frontal gyrus (BA 47), parahippocampal gyrus (BA 36), and medial occipital gyrus (BA 18) in the right hemisphere and the middle temporal gyrus (BA 37), parahippocampal gyrus (BA 36), fusiform gyrus (BA 19), lingual gyrus (BA 19), medial occipital gyrus (BA 19), cerebellar hemisphere, and vermis in the left hemisphere.

Discussion

Two different retrieval tasks from the same memory source, i.e., complex and simple, activated several brain areas. Both tasks activated the bilateral parahippocampal areas, cerebellar hemispheres, medial and inferior occipital areas, and right prefrontal and inferior temporal areas. However, activation of the left prefrontal areas was identified only with the complex retrieval task.

Tulving et al. (1994) proposed the so-called hemispheric encoding/retrieval asymmetry (HERA) hypothesis and emphasized the importance of the right prefrontal cortex for retrieval of episodic memory. However, a recent fMRI study (Nolde et al., 1998a) presented a strong evidence that the left prefrontal cortex is more important for episodic retrieval with memory sources. Thus, Nolde et al. (1998b) reported although episodic retrieval activated bilateral prefrontal areas, only the left prefrontal activity was related to the amount of episodic detail to be remembered. They subsequently argued that, in episodic retrieval, relatively simple processes are subserved by the right prefrontal cortex and the more reflectively demanding and systematic processes are subserved by the left prefrontal cortex. They named this cortical asymmetry of reflective activity (CARA) theory. The theory was also supported by evidences from brain-damaged patients (e.g., Swick & Knight, 1996).

As far as the prefrontal cortex is concerned, the comparison of SR with VI in the present study activated the right prefrontal cortex, which is consistent with Tulving’s hypothesis. However, the comparison of CR with VI activated the bilateral prefrontal cortex, which is consistent with Nolde’s theory. Since our remembering behavior is
a complex process involving many items of different nature, the left prefrontal area must play a critical role in addition to the right.

REFERENCES


32. Activation of the Subcallosal Area of the Anterior Cingulate Correlates with Success in Task Responding: A Positron Emission Tomography (PET) Study

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A $^{15}$O PET study examined the effect of familiarity on rCBF in a picture naming task. During separate scans subjects named pictures of highly familiar objects, less familiar objects or responded yes to abstract patterns. Naming accuracy correlated negatively with rCBF of lateral frontal cortex (BA 10, 45, and 47), suggesting that these areas participate in word search. Conversely accuracy correlated positively with activation in the ventral medial frontal cortex particularly in the subcallosal area of the anterior cingulate (BA 12, 25). Subtraction analyses revealed that the abstract pattern condition activated the subcallosal area more than the familiar picture naming condition indicating that activation in this area was not linked to the emotional valence of the pictures themselves. Rather we suggest that BA 12 and 25 registered the subjects’ response confidence. © 2001 Academic Press

Introduction

Brain imaging studies have shown that frontal lobe activity is augmented with increased demands on the planning and execution stages of cognitive tasks. An important part of a task, however, is postexecutive and involves the comparison of resultant performance with intended goals. Few studies have indicated what brain areas are involved in this response monitoring phase of the task, although Luria (1966) proposed that the comparison of the effect of an action with its program of origin was also one of the regulatory functions of the frontal lobes. Here we report distinctive patterns of frontal lobe activation associated with successful and less successful completion of a simple cognitive task (picture naming) and propose that the areas associated with successful naming are involved in the response monitoring process.
In a positron emission tomography (PET) study using the bolus $\text{H}_2^{15}\text{O}$ methodology, subjects were asked to name pictures of objects which varied in level of naming difficulty from scan to scan. We found that regional cerebral blood flow (rCBF) increased in lateral areas of the frontal cortex as naming difficulty increased and performance accuracy decreased, indicating areas recruited for semantic retrieval. Conversely we found that rCBF increased linearly in the subcallosal area of the anterior cingulate and ventral medial region of the frontal cortex as success in naming performance increased. We propose that these medial frontal areas were registering the subject’s confidence in their responses, with greater confidence producing greater activation.

Methods

Subjects. Fifteen elderly subjects, 7 men and 8 women, without any history of neurological illness, participated in the experiment. Participants’ mean age and level of education in years were, respectively, 73.5 and 12.5.

Procedure. Subjects underwent six scans during which they performed naming tasks. All visual stimuli were presented on a computer monitor at the same rate of one per 2 s with a display time of one second. The stimuli were a series of plus signs in Scan 1 (Baseline) and a series of abstract patterns in Scan 2 (Abstract). Subjects were instructed to respond “yes” to the plus signs and the abstract patterns as they were presented. In Scans 3 to 6, four series of pictures (Easy Animals, Hard Animals, Easy Tools, Hard Tools) were presented, one series during each scan. The order of presentation of the four picture naming series was counterbalanced across subjects. Subjects were instructed to name each picture as it appeared but to go on and name the next picture if they could not name a picture fast enough. An experimenter recorded the subjects’ responses.

Stimuli. The picture stimuli were selected with a view to producing lower naming accuracy on the Hard blocks than on the Easy blocks. Selection of items was based on familiarity ratings and accuracy scores from a normative study carried out with 40 similarly aged subjects. The mean familiarity ratings and accuracy from this normative study for the Easy Animals and the Easy Tools pictures were, respectively, 4.6, 4.7 ($t = 1.3, p = .2$), 96, and 96% ($t < 1$). The mean familiarity ratings and accuracy for the Hard Animals and Hard Tools were: 4.1, 3.8 ($t = 1.9, p = .07$), 70, and 71% ($t < 1$).

Scanning methods and data analysis. PET data were obtained using an ECAT Exact HR+ (CTI/Siemens) tomograph. The distribution of normalized cerebral blood flow (CBF) was measured during each 90-s PET scan using the bolus $\text{H}_2^{15}\text{O}$ methodology (Raichle, Martin, & Markham, 1983). Individual high-resolution MRI studies from a Philips Gyroscan ACS (1.5 T) were also obtained for structural–functional (MRI–PET) coregistration with PET data.

A regression analysis using an analysis of covariance (ANCOVA) was applied to the data to determine regions where CBF increased with either increases or decreases in picture naming accuracy by each subject on each block. Specific subtraction analyses were also carried out; here a $t$ value was calculated at each voxel by dividing the mean CBF difference by its standard deviation pooled across all brain voxels. For both subtraction and regression analyses significant increases in CBF were detected using a method based on 3-D Gaussian random field theory, which corrects for multiple comparisons involved in searching across a volume. During whole brain searches $t$ statistic values equal to or exceeding a criterion of $t = 3.53$ were considered significant ($p < .01$, two tailed).
Results

Behavioral data. The mean response naming accuracy scores (% correct ± SD) during scanning were: Easy Animals 93.5 ± 9.9; Easy Tools 95.3 ± 5.6; Hard Animals 57.3 ± 23.1; and Hard Tools 70.2 ± 18.4. Errors consisted largely in omissions. A two-way repeated-measures ANOVA carried out on the subjects’ picture naming accuracy revealed a main effect of object Familiarity \( F = 77.3, p < .001 \), confirming that subjects were more accurate on the Easy blocks than on the Hard blocks. Subjects were also more accurate naming pictures in the Hard Tools block than those in the Hard Animals block \( F = 5.3, p < .05 \).

PET data. The effect of naming accuracy (or difficulty) was assessed by correlating rCBF for each scan with each subject’s accuracy for each picture naming scan. Both the negative and the positive correlations produced distinctive patterns of activation in the frontal cortex. Whereas naming accuracy correlated negatively with activity in the low lateral and high medial areas (Brodmann Area 6 and 10 on the left and BA 45 and 47 on the right) of the frontal cortex, it correlated positively with rCBF in the ventromedial area of the frontal lobe. Particularly striking was the activation in the subcallosal area of the anterior cingulate (BA 25, 12) predominately on the right.

The Abstract patterns minus Easy Tools and the Abstract patterns minus Easy Animals subtractions produced similar peaks of activation. For both there was a strong center of activation in the subcallosal area of the anterior cingulate (BA 25, 12) and in the medial portion of the orbital gyrus (BA 11) as in the positive correlation analysis.

Discussion

In this experiment, despite a fixed presentation rate, task difficulty varied from very easy (i.e., responding “yes” to the abstract patterns) to quite difficult (e.g., naming Hard Animals where accuracy was 57%). The effect of task difficulty was clearly seen in specific areas of the prefrontal cortex. In lateral areas, rCBF increased when the objects were less familiar and subjects were less accurate. We suspect that activation of these regions reflects more effortful semantic retrieval procedures and “semantic working memory” rather than semantic storage per se (Demb et al., 1995).

In contrast with the activation on the convexity of the cortex, rCBF in medial ventral areas increased linearly with successful picture naming scores (i.e., increases in picture naming accuracy). This is in keeping with the results of a metaanalysis of PET studies (Paus et al., 1998) which revealed that activation of the subcallosal area of the anterior cingulate is frequently related to decreases in task difficulty. We would suggest that this medial pattern of frontal activation reflects the “limbic tone” of the subjects and is as such related to their task success, rather than actual execution of the picture naming task. Lesions in the medial frontal area are not characterized by poorer performance on naming tasks but rather by disturbances in behavioral self-regulation and increases in confabulatory responses (Schnider & Gutbrod, 1999). Furthermore, in our study this medial frontal activation also occurred during Abstract patterns scans (compared with Easy naming scans) indicating that neither object identification nor an emotional content to the stimuli themselves was necessary for activation in this area. This area is extensively connected to the limbic system and is known to play a role in the regulation of autonomic functions. We attribute the activation found in the medial frontal subcallosal region to a kind of response monitor and suggest that the area registers the subjects’ confidence in the responses they are producing.
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