

Subcortical Loop Activation during Selection of Currently Relevant Memories

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Abstract

■ Clinical studies on spontaneous confabulation and imaging studies with healthy subjects indicate that the anterior limbic system, in particular, the orbitofrontal cortex (OFC), is necessary to adjust thought and behavior to current reality. It appears to achieve this by continuously suppressing activated memories that do not pertain to ongoing reality, even before their content is consciously recognized. In the present study, we explored through what anatomical connections the OFC exerts this influence. Healthy subjects were scanned with H₂¹⁵O PET as they performed four blocks of continuous recognition tasks, each block composed of a different type of stimuli (meaningful designs, geometric designs, words, non-words). Within each block, three runs composed of exactly the same picture series, arranged in different order each time, were made. Subjects were asked to indicate item recurrences

only within the currently ongoing run and to disregard familiarity from previous runs. In the combined first runs, in which all items were initially new and responses could be based on familiarity judgement (with repeated items) alone, we found medial temporal and right orbitofrontal activation. In the combined third runs, when all items were already known and selection of currently relevant memories was required, we found left orbitofrontal activation contingent with distinct activation of the ventral striatum, head and body of the caudate nucleus, substantia nigra, and medial thalamus. The study indicates that the OFC influences the cortical representation of memories through subcortical connections including the basal ganglia and the thalamus. The data are compatible with a role of the dopaminergic reward system in the monitoring of ongoing reality in thinking. ■

INTRODUCTION

The human orbitofrontal cortex (OFC) is implicated in olfaction, reward processing, and social behavior (O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001; Bechara, Damasio, & Damasio, 2000; Elliott, Friston, & Dolan, 2000; Rolls, 1996; Damasio, 1994). Human imaging studies indicate a role of the OFC in memory processing (Frey & Petrides, 2000; Elliott & Dolan, 1999). Only recent studies revealed a specific contribution to the ability to select from memory those activated traces that pertain to ongoing reality: Patients having acute damage of the OFC itself or of anterior limbic structures directly connected with it (basal forebrain, amygdala, dorsomedial thalamus, hypothalamus) often act on the basis of previous habits rather than ongoing reality, justify their actions with stories, which appear to be invented but can mostly be traced back to real events (spontaneous confabulations), and are disorientated (Schnider, von Däniken, & Gutbrod, 1996a, 1996b). We have found that these patients fail to distinguish between memories that pertain to ongoing reality and memories that do not (Schnider et al., 1996a, 1996b). This failure appears to emanate from an inability to suppress (deactivate) memory traces that

do not pertain to ongoing reality (Schnider & Ptak, 1999); currently irrelevant memories thus guide their thinking and behavior.

In these clinical studies, we used variations of the following task: Patients made a first learning run of a continuous recognition task, in which they had to indicate picture recurrences (Figure 1). This first run demands distinction between new (unfamiliar) and repeated (familiar) items, namely new learning. Failure in this run did not discriminate between spontaneous confabulators and nonconfabulating amnesic subjects (Schnider et al., 1996a; Schnider & Ptak, 1999). The critical part of the task was the second run, composed of exactly the same picture series, but arranged in different order. Subjects were asked to disregard familiarity from the first run and to indicate picture recurrences only within the current run. This run thus required the ability to distinguish between an item's previous occurrence in the ongoing, rather than the previous run. Nonconfabulating patients with amnesia and healthy controls had no difficulty to maintain their performance in this second run, whereas spontaneous confabulators dramatically decreased their performance (Schnider et al., 1996a; Schnider & Ptak, 1999). They had a steep increase of false positive responses (but not of true positives), even when the second run was made 1 hr after the first run. This increase of false positives in

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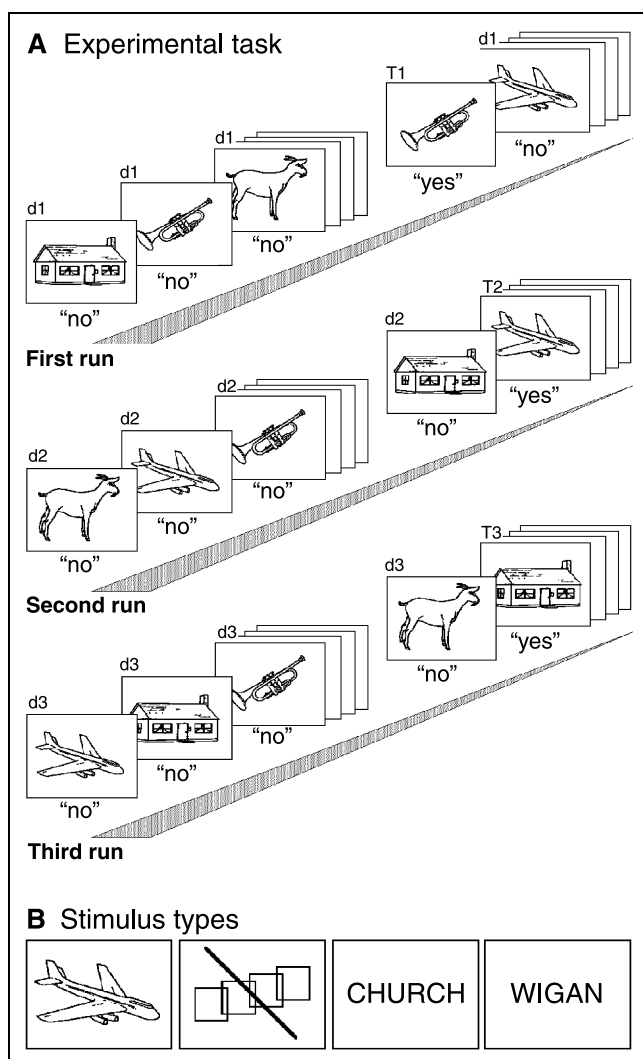


Figure 1. The task. (A) Subjects had to indicate for each item whether it had already appeared within the same, ongoing run; “yes” and “no” indicate correct responses. (B) Stimulus types: meaningful designs (Snodgrass & Vanderwart, 1980), geometric designs, meaningful words, and nonwords. Each block was composed of only one stimulus type. d = distracter; T = target.

the second run was specific for spontaneous confabulation and was also highly predictive of disorientation (Schnider et al., 1996b). Recovery from spontaneous confabulation always paralleled the ability to suppress this interference (Schnider, Ptak, von Däniken, & Remonda, 2000). Whereas most patients were convinced about the correctness of their answers, some complained about their difficulty in distinguishing between the two runs; one patient even started to doubt that any item was truly a recurrence within the second run (Ptak & Schnider, 1999).

The paradigm applied in these studies markedly differs from previously described temporal order and source memory tasks, which demand the ability to attribute a memory to a specific source, context, or time in the past. Failure in such tasks does not have any

specificity for spontaneous confabulation (Johnson, O'Connor, & Cantor, 1997) and may even be seen in nonamnesic subjects with dorsolateral frontal lesions (Kopelman, Stanhope, & Kingsley, 1997; Kesner, Hopkins, & Fineman, 1994; Milner, Corsi, & Leonard, 1991; Shimamura, Janowsky, & Squire, 1990). Our task does not demand distinction between information sources or contexts in the past (Johnson, Hashtroudi, & Lindsay, 1993; Johnson & Raye, 1998), rather it demands the ability to refer a memory evoked by the repeated presentation of an item to its own previous occurrence—either in the current run, the “now,” or a previous run (Schnider, 2001).

The distinction between our paradigm and common temporal order tasks is not only supported by its behavioral specificity, but also by its anatomical specificity. Spontaneous confabulation persisting beyond the phase of a confusional state (delirium), which was always linked to failure in our task, results from lesions involving anterior limbic structures, more specifically, lesions of the OFC or structures connected with it: basal forebrain (Burgess & McNeil, 1999; Johnson et al., 1997; Schnider et al., 1996a; DeLuca & Cicerone, 1991), amygdala and perirhinal cortex (Schnider et al., 1996b; Schnider & Ptak, 1999), dorsomedial thalamus (Gentilini, De Renzi, & Crisi, 1987) or its connections with the OFC in the capsular genu (Schnider, Gutbrod, Hess, & Schroth, 1996), or the medial hypothalamus (Ptak et al., 2001). Considering these lesion sites and the patients' performance in our task, we suggested that the anterior limbic system, in particular, the medial OFC, provides a mechanism that refers thinking to ongoing reality by suppressing (deactivating) memories that do not pertain to current reality (Schnider & Ptak, 1999).

The conclusions from these clinical studies were refined in imaging and evoked potential studies. Healthy subjects performing the first run of the task while being scanned with $H_2^{15}O$ -PET had strong activation of the parahippocampal gyrus bilaterally and discrete activation of the right anterior medial OFC (Schnider, Treyer, & Buck, 2000). By contrast, as the subjects performed a repeated (third) run of this task, they had strong, primarily left-sided, posterior medial OFC activation, whereas the medial temporal lobe did not activate any more. This activation was consistent with the lesions provoking spontaneous confabulation, but it clearly differed from the frontal convexity activations seen in studies on source monitoring or retrieval of episodic detail (Ranganath, Johnson, & D'Esposito, 2000; Rugg, Fletcher, Chua, & Dolan, 1999; Nolde, Johnson, & D'Esposito, 1998).

An evoked potential study with healthy subjects indicated that selection of currently relevant memories, as measured in the second run of our task, is a relatively early process (Schnider, Valenza, Morand, & Michel, 2002). In the first learning run, the electrical cortical response to items' first presentation (nontargets or

“distracters”) and subsequent reappearance (“targets”) differed by amplitude modulation between 300 and 600 msec (with statistically significant amplitude differences between 400 and 480 msec). This corresponds to potential amplitude differences at 300–500 msec observed in other studies on recognition memory (Tsivilis, Otten, & Rugg, 2001; Ranganath & Paller, 1999; Friedman, 1990). Amplitude modulation was weaker in the second run, in which all items were already known. However, nontargets of the second run (“distracters,” i.e., the items whose interference spontaneous confabulators had failed to suppress) provoked a distinctly different, early electrical cortical response, which differed from all other items (distracters and targets of the first run, targets of the second run) by a specific loss of a cortical map configuration, associated with a distinct alteration of a frontal potential, after 220–300 msec (Schnider et al., 2002). Thus, it appears that the anterior limbic suppression mechanism, which refers thought to ongoing reality, adapts the cortical representation of memories—as reflected in the electrical map configuration—at a relatively early stage (220–300 msec), even before a memory’s content is consciously recognized (>400–480 msec).

How does the OFC influence activity in the neocortex and “suppress” (deactivate) currently irrelevant memories? Known anatomical connections suggest that the OFC might communicate with wide areas of neocortex through frontal–subcortical loops involving the basal ganglia and the thalamus (Joel & Weiner, 2000; Alexander, DeLong, & Strick, 1986). In the present study, we used an experiment based on the same paradigm as our previous PET study, but we increased the power of the task by making four (instead of one) blocks of the task, composed of four different stimulus types (instead of meaningful pictures only): meaningful line drawings (Snodgrass & Vanderwart, 1980), meaningless geometric designs, meaningful concrete nouns, and pronounceable nonwords (Figure 1). Our specific interest was to explore whether this adaptation of the task would indeed induce activation of subcortical structures known to connect the OFC with the neocortex. Since the posterior OFC and the basal forebrain—key regions for the present study—are particularly prone to the susceptibility artifacts of functional MRI (fMRI; Ojemann et al., 1997), we used H₂¹⁵O PET rather than fMRI.

RESULTS

Eight subjects participated in the study. All of them indicated that they experienced the task as challenging. Nonetheless, they performed near ceiling in both scanned runs: Hit rate was 19.1 ± 0.94 ($95.5 \pm 4.7\%$), median 19 (95.5%), in the first run and 18.5 ± 1.8 ($92.5 \pm 9\%$), median 19 (95.5%), in the third run (Wilcoxon signed rank test, nonsignificant). False positives rose

from 1.2 ± 1.8 ($3 \pm 4.5\%$) in the first run to 2.4 ± 2.7 ($6 \pm 6.8\%$) in the third run. Although this difference was significant ($p < .01$), it was also too small (median 1–2.5% in both runs) to allow for correlation analyses of performance with brain perfusion. False responses in the baseline task were exceptional.

Learning (Run 1–Baseline)

Areas of significant activation in the first run relative to the baseline task are shown in Figure 1A and summarized in Table 1. As expected, initial encounter with the stimulus series led to strong activation of the medial temporal lobe on both sides, including the parahippocampal and fusiform gyri on both sides and the hippocampus proper on the right side, with extensive coactivation of occipital visual cortex on both sides. In addition, there was a strong cluster of activation centered on the transition of the right posterior OFC and anterior inferior insula to the perirhinal cortex. A weaker activation was found in the left anterior medial OFC with extension into the anterior inferior insula. In addition, there was a cluster of strong activation in the right mesencephalon’s transition to the posterior medial thalamus.

Selection of Currently Relevant Memory Traces (Run 3–Baseline)

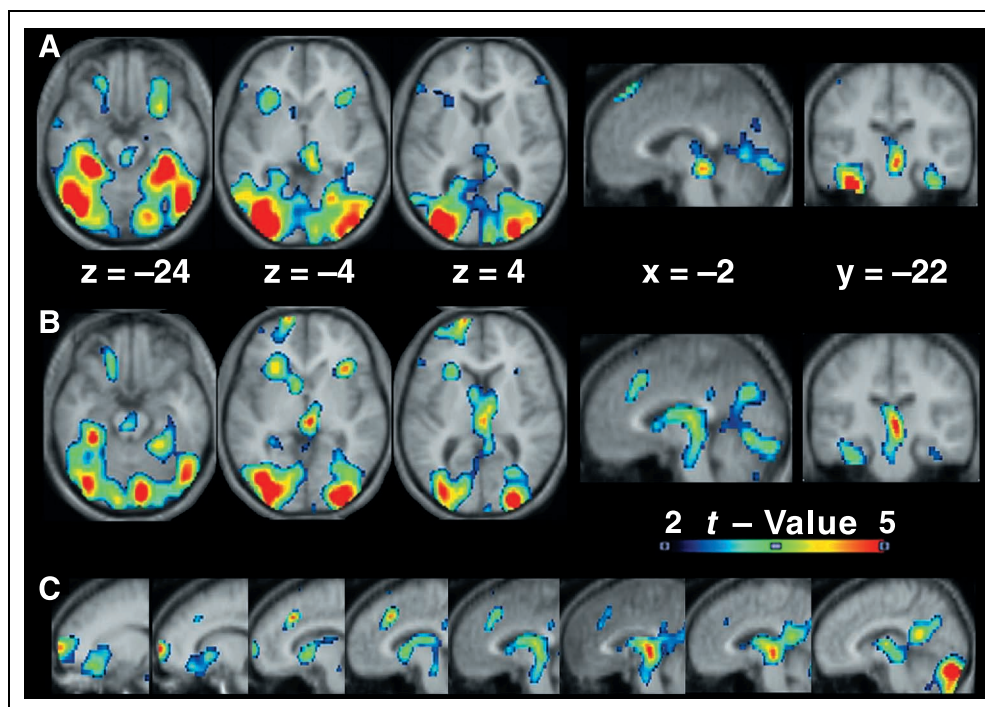
In comparison with the first run (Figure 2A), the third run provoked discretely stronger anterior limbic activation (left OFC, bilateral anterior inferior insula), whereas medial temporal and occipital activation was markedly weaker (Figure 2B, run 3–baseline). In particular, however, the subcortical activation, which was very discrete in the first (learning) run (Figure 2A, run 1–baseline), was now distinctly more manifest and coherent: As Figure 2C displays, the left OFC activation is contiguous with the activation of the head and body of the left caudate nucleus and extends down to the level of the mesencephalon (encompassing substantia nigra and ventral tegmental area). This deep activation continues

Table 1. Contrast of Run 1–Baseline

<i>Region</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>t Value</i>
Left parahippocampal gyrus	–34	–34	–32	7.81
Right parahippocampal gyrus	36	–36	–24	6.07
Right hippocampus	24	–12	–32	3.40
Right orbitofrontal–perirhinal cortex	32	16	–24	4.09
Left orbitofrontal cortex	–20	38	–24	3.39
Substantia nigra	2	–28	–16	5.13

The *x*, *y*, and *z* values indicate the MNI coordinates of the clusters’ maximal activity.

Figure 2. Areas of activation in comparison with the baseline task. (A) Learning run (run 1–baseline); (B) run requiring memory selection (run 3–baseline). The x , y , and z coordinates refer both to A and B. (C) Sagittal cuts from left to right for the comparison of run 3–baseline.



on the right side up the paramedian thalamic area, encompassing in any case the dorsomedial thalamic nucleus. Table 2 lists the areas of significant activation in run 3 compared to baseline.

Comparison Between Learning (Run 1) and Memory Selection (Run 3)

The third run of the present experiment differs from the first run in that all items are already known from two presentations. Thus, whereas the first run primarily depends on new learning and familiarity judgment, the second run depends primarily on the distinction between currently relevant and currently irrelevant memories (suppression of items seen in the previous rather than the current run). This difference between the runs is subtle in comparison with the commonalities

between them: All runs are composed of the same item series, have exactly the same design (same number of targets), and even have the same task instruction. Not surprisingly, our previous imaging study had already shown that the increase in anterior limbic activation is very discrete from the first to the third run (Schnider, Treyer, et al., 2000). A direct comparison between the runs further risks to obfuscate essential components of the cognitive networks common to all runs of the task. Notwithstanding these caveats, a direct comparison of the two runs is shown in Figure 3. As expected from the previous study, the first run provokes stronger activation in medial temporal areas, in particular, the perirhinal and parahippocampal cortex on both sides (Figure 3A). The right perirhinal activation extends into the OFC. The difference in these clusters meets our criterion of significance ($t > 3$). In addition, outside the area covered by our a priori hypothesis, the left inferior temporal cortex and posterior insular cortex appear to have stronger activation.

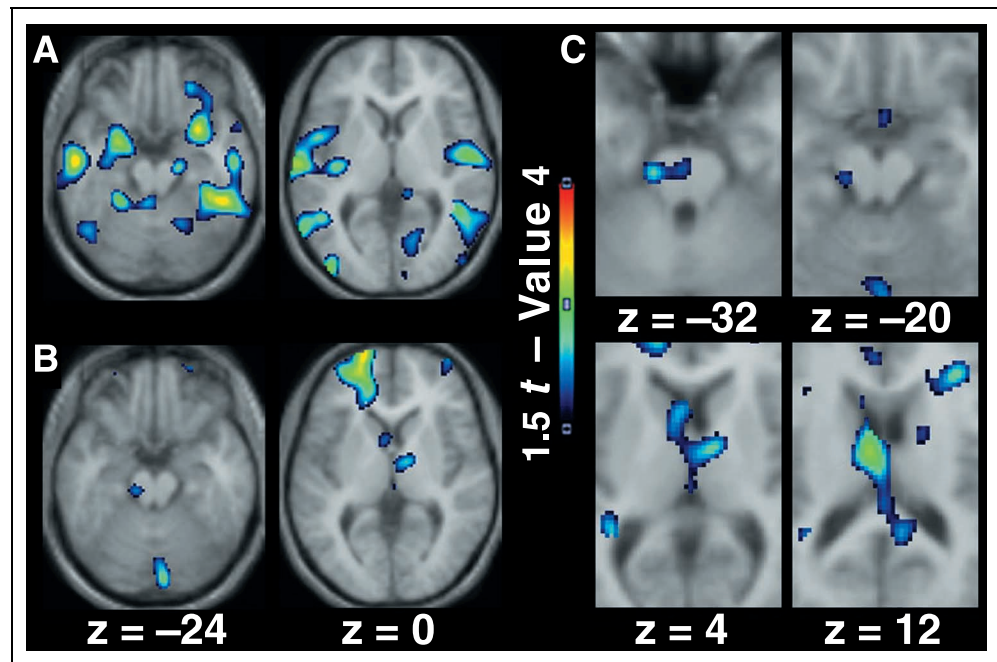
The increase of activation from the first to the third run (Figure 3B,C) is discrete but consistent with the conclusions based on the comparison of the third run with baseline: There is increased activation of subcortical structures, in particular, the head and body of the left caudate nucleus (Figure 3B and C, lower row), the lateral and inferior part of the left substantia nigra (Figure 3C, upper row), and the medial thalamus (Figure 3B and C, lower left), possibly also the anterior medial hypothalamus (Figure 3C, upper right). Only the activation increase of the caudate body attains our criterion of significance ($t > 3$); the other differences have to be considered as trends. In addition, outside the

Table 2. Contrast of Run 3–Baseline

Region	x	y	z	t Value
Left orbitofrontal cortex	–18	30	–20	3.70
Left anterior insula	–28	24	–4	4.32
Right anterior insula	38	24	–8	4.91
Left caudate (head)	–8	6	–4	3.91
Substantia nigra	–4	–26	–24	3.22
Right medial thalamus	4	–26	–4	5.05

The x , y , and z values indicate the MNI coordinates of the clusters' maximal activity.

Figure 3. Direct comparison between runs. (A) Run 1–run 3; (B, C) run 3–run 1, with (C) detailing subcortical activation in the comparison run 3–run 1.



area covered by our a priori hypothesis, there is markedly increased activation of the left frontopolar region (Figure 3B).

DISCUSSION

This study confirms and extends findings from previous lesion and imaging studies using a similar paradigm. Similar to our previous PET study, which had only one block (including one baseline and two recognition runs) with one stimulus type (color photographs), new learning of information, as demanded in the first run of the task, activated medial temporal structures and the OFC, in particular, the right OFC. In comparison with this first run, the selection of currently relevant from a series of already familiar information, as demanded in the third run, discretely augmented activation of the OFC, in particular, the left posterior medial OFC, whereas medial temporal activation markedly decreased. Thus, these findings agree with our previous imaging study (Schnider, Treyer, et al., 2000). However, the new finding of the present study, which has a more powerful design (four blocks with different stimulus types), is that this selection process is associated with activation of subcortical structures that are contiguous with the left OFC activation and involve the left caudate nucleus (ventral striatum, head, and body of the caudate), the left substantia nigra and ventral tegmental area, and the right medial thalamus. These structures are known to participate in frontal–subcortical loops connecting the OFC with itself and prefrontal neocortex (Middleton & Strick, 2000; Haber, Kunishio, Mizobuchi, & Lynd-Balta, 1995; Alexander et al., 1986) and to contain the dopaminergic structures modulating activity in the loops

(Joel & Weiner, 2000). To our knowledge, this is the first direct demonstration of an orbitofrontal–subcortical loop activation in a memory task.

The findings suggest a flexible participation of the OFC in memory processing. Largely overlapping parts of the posterior OFC participated in both runs. As in our previous study, there was a tendency of the right OFC to be more activated during the first (learning) run, and of the left posterior medial OFC to be activated in the third (selection) run. It is possible that the precise focus of maximal OFC activation varies depending on the familiarity with the stimuli (Schnider, Treyer, et al., 2000). In any case, it appears that the posterior medial OFC contributes both to new learning and selection of currently relevant memories, as tested by our task. This interpretation agrees with clinical observations: Most patients with medial OFC lesions—similarly with patients having medial temporal lesions—also failed in the first run of a similar, albeit much easier, task (Schnider et al., 1996a; Schnider & Ptak, 1999).

All patients with medial OFC lesions involved in our clinical studies confabulated spontaneously and were disorientated in the acute stage; that is, they acted on the basis of previous habits disregarding their present brain damage. Whereas some patients performed normally in the first run, all of them drastically decreased their performance in the second run; they had a steep increase of false positives (Schnider et al., 1996a; Schnider & Ptak, 1999). It is important to note that the task used in these clinical studies was considerably easier than the one used in the current study: A small number of items was repeated up to five times during a run (present study: an item is repeated no more than twice), and the runs were separated by up to 1 hr

(present study: 1 min). The increase of false positives in the second run was specific for spontaneously confabulating patients and reliably distinguished them from nonconfabulating amnesics and normal controls. As they ceased to confabulate and regained the ability to base their behavior on true ongoing reality, this decrease of performance in the second run disappeared, although some patients continued to fail in the first run; that is, they remained amnesic (Schnider, Ptak, et al., 2000). Thus, OFC lesions may impair new learning (thus provoking amnesia), produce an inability to suppress currently irrelevant memories (thus provoking spontaneous confabulation), or both. The present imaging study fails to separate distinct areas within the OFC contributing specifically to one, rather than the other, of these memory functions. Indeed, it appears likely that these functions are mediated by overlapping, rather than distinct, areas of the OFC.

Activation of the right rostral OFC has previously been observed as subjects learned a series of new abstract visual patterns (Frey & Petrides, 2000), indicating that the OFC participates in the acquisition of new information. Another study described activation of the medial OFC and head of the caudate nucleus bilaterally in a delayed matching-to-sample task (DMS), in which subjects hold a complex visual pattern for 5–15 sec in memory before selecting the same item from a pair (Elliott & Dolan, 1999). Our task constitutes a DMS task, but a very complex one: Any item appearing during a test run may potentially reappear during the run. Thus, from the perspective of the test subject, an unknown number of items has to be held on-line for an indefinite length of time, until the end of the test run. This requirement is similar in both runs. The specificity of the task for the monitoring of ongoing reality—the capacity whose failure produces spontaneous confabulation and disorientation (Schnider & Ptak, 1999)—lies in the need to suppress false positives in response to distracter items (first presentations within the ongoing run) in the runs following the first one. This specific task requirement was also demonstrated in an evoked potential study with healthy subjects: The main difference between the first and the second run was a strikingly different early cortical potential in response to distracters of the second run (220–300 msec) (Schnider et al., 2002). For the present study, these observations indicate that only 60% of the items presented in the third run (distracters) have the potential of producing the difference in PET activation specific for the task component of interest: the selection of currently relevant memories. Theoretically, this weakness of our method might be overcome by using event-related fMRI instead of PET. However, fMRI sequences are extremely susceptible to artifacts in the area of the posterior OFC, so that either no or only a heavily distorted signal can be obtained from the area of interest for this study. PET does not have such artifacts.

Given these limitations, the subcortical activation obtained in run 3 is all the more astonishing. Our present search for this activation differed from our previous imaging study in two respects (Schnider, Treyer, et al., 2000): First, rather than using only one stimulus type (color photographs), we used four different types of stimuli (meaningful designs, meaningless geometric designs, concrete words, nonwords). Each block of the experiment was composed of only one stimulus type in order to create as little interference as possible between, but as much as possible within the blocks (between runs 1 and 3). Using four different stimulus types may have activated more components of the reality monitoring system explored here. Most importantly, however, this design yielded four measurements of activation per run, rather than one, thus considerably increasing the statistical power.

The subcortical activation found in the third run of this experiment perfectly agrees with our hypothesis on how the posterior OFC communicates with the neocortex to influence the cortical representation of active memory (Schnider, 2001). The hypothesis was based on two lines of evidence. First, spontaneous confabulation does not only result from OFC lesions, but also (and foremost) from lesions of the basal forebrain (which contains the ventral striatum) (Burgess & McNeil, 1999; Ptak & Schnider, 1999; Johnson et al., 1997; Schnider et al., 1996a; DeLuca & Cicerone, 1991), the medial thalamus (Gentilini et al., 1987) or disconnection between the thalamus and the OFC from interruption of the inferior thalamic peduncle (Schnider et al., 1996). Additional lesions sites are the medial hypothalamus (Ptak et al., 2001; Kahn & Crosby, 1972) or the combined lesion of the amygdala on one side and the perirhinal cortex on the other side (Schnider et al., 1996), structures that have close connections with the posterior OFC. Thus, clinical studies clearly indicate that subcortical structures other than the OFC are involved in the selection of currently relevant memories. A second basis for the hypothesis was the known anatomical connections: The OFC has strong connections through the ventral striatum, the pallidum, substantia nigra (pars reticulata), and the dorsomedial thalamic nucleus back to the prefrontal cortex, including the OFC itself (Middleton & Strick, 2000; Haber et al., 1995; Percheron, Yelnik, Francois, Fenelon, & Talbi, 1994; Alexander et al., 1986). This loop is under modulatory influence from the dopaminergic system in the substantia nigra (pars compacta), the ventral tegmental area, and the ventral striatum (Joel & Weiner, 2000). Thus, the OFC not only participates in a cortico-subcortical loop, but also projects onto the dopaminergic system modulating the activity of the loop. As discussed elsewhere (Schnider, 2001), we suspect that the ability to adapt thinking to ongoing reality; that is, the ability to suppress activated memories that do not pertain to current reality has similarities with the ability of animals to suppress

(extinguish) their previous habit of reacting to stimuli that were previously, but no more now, rewarded. In extinction trials, specific neuronal responses were obtained in OFC, ventral striatum, ventral tegmental area, and substantia nigra (pars compacta) (Schultz, Tremblay, & Hollerman, 2000; Thorpe, Rolls, & Maddison, 1983; Rosenkilde, Bauer, & Fuster, 1981). The activity found in the present study includes all of these structures (parts of the loops as well as the components of the dopaminergic system). Although PET does not allow to demarcate these individual structures, the present study demonstrates basal ganglia and medial thalamic participation in a vital capacity: the ability to refer thinking to ongoing reality.

METHODS

Subjects

The test subjects were eight male right-handed students aged 20–31 years who gave written informed consent and were paid to participate in the study. The study was approved by the local Ethical Committee and the Swiss Federal Bureau of Radiation Protection.

Task

The design of the task is explained in Figure 1. Four different blocks were composed, each consisting of a different set of items from one of the following categories: meaningful line drawings (Snodgrass & Vanderwart, 1980); meaningless geometric designs; meaningful concrete nouns; and pronounceable nonwords. Each of the four blocks had the same design: a first, second, and third continuous recognition run composed from the same series of items, presented in different order each time, then one run of the baseline task.

Within the blocks, each run of the continuous recognition task had the same design: The subjects saw 60 items, one after the other, and were requested to indicate item recurrences within the test run. Unknown to them, the series was composed of 40 items, among which 12 were selected during the run to reappear once (four items) or twice (eight items) as a target (total, 20 item recurrences within a run). Stimuli were presented for 3 sec on a TV screen, interstimulus interval was 1 sec. Thus, a test run lasted for 240 sec. Subjects were asked to indicate item recurrences within the currently ongoing run as fast as possible by pressing a mouse button with their right hand, whereas they should not press the button if the item appeared for the first time within the current test run. The baseline task consisted of the repeated presentation of two new items of the current block's stimulus category (3 sec; interstimulus interval, 1 sec). The subjects were asked to indicate immediate item recurrences with a button press, whereas they should not press when the item changed. The number of immediate item recurrences during the baseline task

was similar to the item recurrences (targets) in the continuous recognition task.

Subjects made the four blocks within a single PET session. The sequence of the four blocks was counter-balanced over the subjects. Runs within a block were separated by a 90-sec break. Before the second and third run of each block, subjects were reminded that they should forget that they had already seen each item and that they should only indicate item recurrences within the upcoming run. Brain activation was measured in the first and third run. Six minutes after the third run of each block (necessary to wash out radioactivity), the baseline task was made and brain activity scanned. The four blocks were separated by 10-min breaks.

Image Analysis

PET scans were acquired on a whole-body scanner (Advance GE Medical Systems, Waukesha, WI) in three-dimensional mode with a 15-cm axial field of view. For each scan, 300–350 mBq $H_2^{15}O$ was administered as a slow bolus with a remotely controlled injection device. PET counts were recorded over 60 sec after the arrival of the bolus in the brain. A 10-min transmission scan was performed between the second and third block. Attenuation corrected data were reconstructed into 35 image planes (slice thickness, 4.25 mm; matrix, 128×128 ; pixel size, 2.34 mm). The accumulated radioactivity counts over 60 sec were taken as measure for cerebral blood flow. Statistical parametric mapping was performed as follows: First, head movement between the scans was corrected using the least squares method implemented in statistical parametric mapping software, SPM99 (Friston et al., 1995). Then, all images of each subject were summed and transformed into stereotaxic space (Montreal Neurological Institute [MNI] coordinates as provided by SPM99). The normalization included linear transformations and deformations based on nonlinear basis function. The resulting transformation matrix was subsequently used to transform each individual scan. Proportional scaling was applied for global normalization to remove global effects. To ameliorate residual interindividual anatomical and functional differences after spatial normalization, the scans were smoothed with a Gaussian filter of 15 mm FWHM. The difference between conditions (first run–baseline; third run–baseline) was then evaluated voxel by voxel in a PET multisubject design. In this design, all 12 scans (four first runs, four third runs, four baseline runs) were included from every subject. The T-contrasts (first run–baseline; third run–baseline) were determined by weighting the four scans of every condition equally. Because we had a clear anatomical hypothesis, we used *t* values uncorrected for multiple comparisons and accepted significance when $t > 3$ ($p < .001$).

An anatomical 3-D SPGR T1-weighted whole-brain magnetic resonance image ($0.94 \times 0.94 \times 1.5$ mm

voxels) was acquired on a GE Signa Horizon EchoSpeed 1.5 T scanner (GE Medical Systems) from every subject and coregistered to the subjects mean PET image so that the evaluated normalization matrix could be applied to the mean anatomical image in parallel to the PET images.

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