

Human Thought and the Lateral Prefrontal Cortex

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Abstract Human thought is a remarkable evolutionary achievement and one of our species' defining abilities. It has been closely linked to the prefrontal cortex (PFC) by converging evidence from a wide range of disciplines, from phylogenetic and ontogenetic development, to patient studies and single-cell recordings, to modern neuroimaging. Here I review work on the links between the lateral PFC and two different forms of thought: goal-directed and spontaneous. A special emphasis is placed on the anterior (rostral or frontopolar) lateral PFC, which supports some of the most complex and uniquely human forms of thought, such as reasoning about multiple relations and introspective cognition, and also becomes recruited during the kind of unconstrained thought processes that occurs during rest. I outline an organizational view of the lateral prefrontal cortex which recognizes different lateral prefrontal subregions as functionally distinct and arranged in a rostrocaudal gradient of complexity in processing and representational abstraction, with higher abstraction in thought corresponding to more anterior lateral PFC regions. Furthermore, it appears that the functions of lateral PFC extend beyond goal-directed thinking, to include more spontaneous, free-flowing mental cognition. Unlike goal-directed thought, however, spontaneously occurring thought appears to draw most heavily upon resources outside the PFC, including lateral and medial temporal lobe regions. The nature of interactions between lateral PFC and the temporal lobe remains an important topic for future research that promises to help elucidate some of the most intriguing aspects of human thought, including its spontaneous generation.

1 Introduction

The lateral prefrontal cortex is known to be essential for human thought and complex cognitive processing. Numerous patient studies have shown that the prefrontal cortex is essential for the complex cognitive processes underlying reasoning and

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E. Kraft et al. (eds.) *Neural Correlates of Thinking*,
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problem solving (Luria 1966; Milner 1963, 1964). Neuroimaging studies have supported this view by demonstrating prefrontal cortex activation across many reasoning tasks (Berman et al. 1995; Baker et al. 1996; Nagahama et al. 1996; Owen et al. 1996; Goel et al. 1997, 1998, 2000; Prabhakaran et al. 1997, 2000; Rao et al. 1997; Goldberg et al. 1998; Osherson et al. 1998; Ragland et al. 1998; Dagher et al. 1999; Goel and Dolan 2000; Wharton et al. 2000).

Although the link between human thought and lateral prefrontal cortex function has been clearly established, this link has been formulated mostly at the general level, and a breakdown of the lateral prefrontal cortex into separate functionally distinct regions has proved to be somewhat more difficult. Nonetheless, one approach to a more precise functional definition has been to regard the prefrontal cortex as a heterogeneous region, comprising specialized subregions with different functional roles. Indeed, cytoarchitectonic studies at the beginning of the twentieth century (Brodmann 1908; Campbell 1905; Elliott Smith 1907; Vogt 1906), as well as recent neuroanatomic (Pandya and Barnes 1987), neurophysiological (di Pellegrino and Wise 1991; Rosenkilde 1979), and neurocircuitry (Alexander et al. 1986; Barbas and Pandya 1991; Pandya and Barnes 1987) studies have suggested that the prefrontal cortex should be subdivided into several structurally and functionally different subregions. A number of regional specifications have been proposed, from Broca's original localization of the inferior prefrontal cortex as an area essential for the production of speech, to recently proposed functional specializations of specific prefrontal subregions such as the ventromedial (Damasio et al. 1996), orbitofrontal (Rolls 1996), and dorsolateral (Goldman-Rakic 1987; Petrides 1991). Some analyses have focused on contrasting one subregion relative to another (D'Esposito et al. 1998; Owen et al. 1996; Petrides 1994), in order to clarify the type of processing for which each subregion is specialized.

Some of the most recent findings from functional neuroimaging have focused precisely on clarifying the functional organization of the lateral prefrontal cortex and linking its different subregions to specific thought processes. Several relevant studies and analyses are described in this chapter, which converge to indicate a rostrolateral (or anterior-to-posterior) organization within the lateral prefrontal cortex, with complex, abstract thought processes represented in the anteriormost regions, and concrete, externally oriented thought processes distributed more posteriorly in the prefrontal cortex. This organization applies for multiple domains of higher cognitive functions, including reasoning, working memory, and episodic memory retrieval, and suggest a specific organization of thought in the human brain. Finally, implications for human thought and cognition are discussed, with emphasis on those processes and prefrontal cortex subregions that bear uniquely human capacities such as higher-order relational reasoning and introspective thought.

2 Higher-Order Relational Reasoning

Higher-order relational reasoning is a specific kind of mental computation that develops slowly in humans and that developed so late in primate evolution as to be unique to humans. Such higher-order relational reasoning involves the processes

of relational integration, or considering multiple relations simultaneously. Children under 5 years of age can solve 0- and 1-relational problems, but fail to solve 2-relational problems that demand integration of multiple relations, even when matched for working memory load to the 1-relational problems (Halford 1984). Nonhuman primates can solve 1-relational problems, but cannot solve problems that require processing multiple relations simultaneously (reviewed in Tomosello and Call 1997). Robin and Holyoak 1995 proposed that failures in relational integration may be attributable to the relatively slow frontal lobe maturation in humans (as indexed by myelination and other markers of cortical development) and to the great expansion of frontal cortex in human evolution. Such ontogenetic and phylogenetic developmental evidence supports the hypothesis that the prefrontal cortex has a selective role in the process of relational integration.

A number of neuroimaging studies (Christoff et al. 2001; Kroger et al. 2002; Bunge et al. 2004) have investigated the specific contribution of prefrontal cortex to higher-order relational reasoning, and the process of relational integration in particular. Here we focus on one of these studies (Christoff et al. 2001), which illustrates and summarizes the main findings. To investigate the process of higher-order relational reasoning, we used functional magnetic resonance imaging (fMRI) to examine brain activation in healthy volunteers during 0-relational, 1-relational, and 2-relational problems adapted from the Raven's Progressive Matrices test. The relational complexity of each problem was defined as the number of relations that had to be considered simultaneously in order to solve the problem. Verbal protocol and eye-movement analyses have shown that Raven's Progressive Matrices problems are solved using a sequential, reiterative strategy for inducing and encoding the rules or relationships of change within each problem Carpenter et al. 1990. Thus, the method we employed for defining the number of relations in each problem had been shown to be valid both psychologically Carpenter et al. 1990 and neuropsychologically Waltz et al. 1999.

Our goal was to test whether prefrontal cortex has a selective role in the process of relational integration in healthy young volunteers, and to determine whether specific prefrontal cortex subregions mediate this role. We hypothesized that increases in prefrontal cortex activation would be specific to the 2-relational problems and would be observed independently of increases in duration of processing. We used an event-related procedure that allowed randomized presentation of different problem types, so that participants were unable to anticipate what type of problem would be presented next. In addition, the duration spent working on each problem was recorded and used in modeling each event-related response. In this way, we were able to identify regions activated by novel processes separately from regions activated by longer engagement of processes common to solving all problem types.

Problems had the general form of the Raven's Progressive Matrices Raven 1938. Each problem consisted of a 3×3 matrix of figures, with the bottom-right figure missing (Fig. 1). After considering the relationship among the given matrix figures, participants had to infer the missing figure and select it among the four alternatives presented on the right side of the matrix.

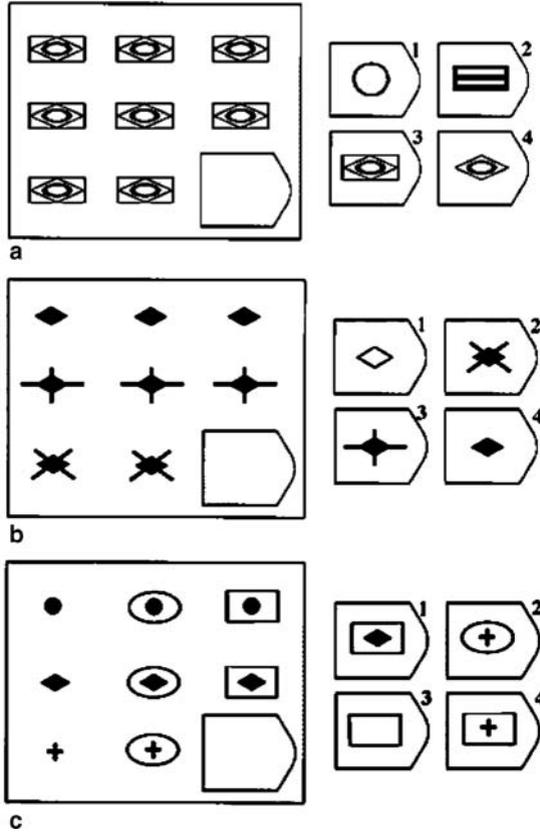


Fig. 1 Examples of problem types used in the experiment

Three different types of problems were created: 0-relational, 1-relational and 2-relational. The 0-relational problems (Fig. 1a) involved no relationship of change and required no relational processing in order to be solved. The 1-relational problems (Fig. 1b) involved a change in either the horizontal or the vertical dimension and, therefore, required processing of a single relation. Finally, the 2-relational problems (Fig. 1c) involved two relations of change, in both the horizontal and the vertical direction. Inferring the correct answer required considering the converging change along both dimensions. Thus, the 2-relational problems required that two relations be integrated, or considered simultaneously.

Behavioral results showed that participants were highly accurate, with 93.8% overall accuracy. Increasing relational complexity resulted in reduced accuracy and slower latency of response.

The activation maxima from the primary analysis using the response-time-convolved hemodynamic response function are illustrated in Fig. 2. No voxels surviving the $p < 0.001(Z > 3.09)$ threshold at the voxel level were revealed in the

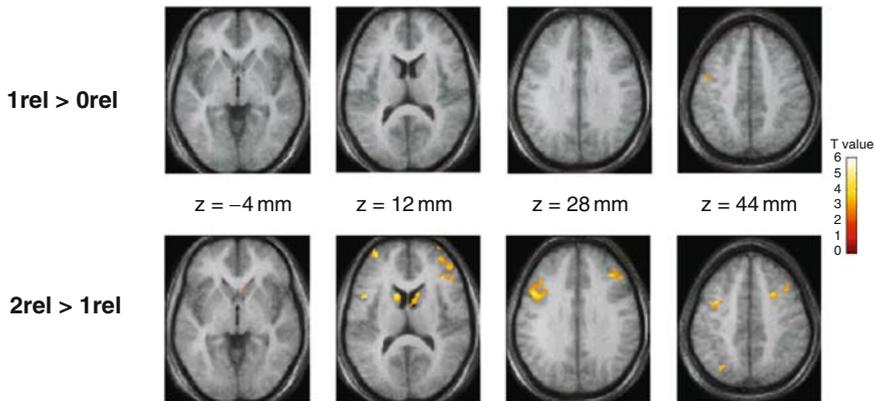
RT-convolved HRF

Fig. 2 Results from voxelwise analysis. *RT* response time; *HRF* hemodynamic response function

1-relational and 0-relational comparison. Two small clusters in the premotor cortex approached significance when the voxel threshold was relaxed to $p < 0.01$, but there were no prefrontal cortex differences even at this level.

The 2-relational and 1-relational comparison yielded activation in the prefrontal cortex bilaterally. There were two left-lateralized cortical regions of activation. The first was a cluster in the left posterior and premotor prefrontal cortex, extending over the inferior prefrontal and precentral gyri, including Brodmann areas (BA) 44 and 6. The second cluster was located in the left anterior prefrontal cortex, extending over the rostrolateral prefrontal cortex, including the lateral portion of BA10. The activation maxima in both of these left prefrontal cortex regions survived correction for multiple comparison (correction was performed using a mask of all prefrontal cortex voxels showing a significant main effect of reasoning).

The right-lateralized regions of activation for this comparison included the dorso-lateral prefrontal cortex, including BA9 and BA46, with maxima of activation in the middle frontal gyrus. At a lower threshold level ($p < 0.01$), the two clusters merged into a single large right prefrontal cortex cluster of activation, extending in anterior direction to include the rostrolateral prefrontal cortex (lateral BA10).

In addition to prefrontal cortex activations, the 2-relational and 1-relational comparison yielded robust activation in the head of the caudate nucleus bilaterally. No other suprathreshold activations were observed for this comparison.

The results revealed a consistent pattern: prefrontal cortex activation was specific to the comparisons between 2- and 1-relational problems, and was not observed in the comparisons between 1- and 0-relational problems. In left rostrolateral prefrontal cortex, this pattern continued to hold even after equating for response time and accuracy among problem types. These results converge with the patient findings of Waltz et al. 1999 and support the hypothesis that prefrontal cortex is selectively involved during the process of relational integration. The results are also

consistent with the view that prefrontal cortex is preferentially engaged during relationally complex processes Robin and Holyoak 1995 and confirm that, as proposed by Halford et al. (1998), the relational complexity of a task can be successfully used to predict prefrontal cortex recruitment.

Rostrolateral prefrontal cortex activations have been observed during highly complex tasks across a wide range of domains. On the basis of a review of studies reporting activation in this region (Christoff and Gabrieli 2000), we have proposed that it may be selectively involved in active processing, such as manipulation or evaluation, performed upon self-generated information. The present findings bear interesting implications relating to this hypothesis and are consistent with it: The relational information associated with a problem from the Raven's Progressive Matrices test is not given in the problem, but has to be inferred, or self-generated, on the basis of given information (the individual object features such as shape, texture, and size). The observed link between rostralateral prefrontal cortex activation and the process of relational integration, therefore, could be due to the associated process of manipulating the self-generated information about the change among objects.

3 Rostrocaudal Organization Within the Lateral Prefrontal Cortex

Most considerations of regional specialization within the prefrontal cortex have concentrated on the posterior prefrontal cortex, including the dorsolateral, ventral, medial, and orbitofrontal regions. There has been far less consideration of the anteriormost part of the prefrontal cortex, usually referred to as the frontopolar (or rostralateral) prefrontal cortex. With remarkable frequency, however, functional neuroimaging studies have detected frontopolar cortex activation when people perform complex cognitive tasks. Activation in this region has been reported for many reasoning tasks, such as the Tower of London task (Baker et al. 1996), the Wisconsin Card Sorting Test (Berman et al. 1995; Goldberg et al. 1998; Nagahama et al. 1996), inductive and probabilistic reasoning tasks (Goel et al. 1997; Osherson et al. 1998), and the Raven's Progressive Matrices test (Prabhakaran et al. 1997). Frontopolar activations are also common when people perform memory tasks involving episodic retrieval (for reviews, see Cabeza et al. 1997; Nolde et al. 1998; Nyberg et al. 1996). Many of these studies report both dorsolateral and frontopolar activations, but few offer suggestions as to what different psychological operations are mediated by these anatomically distinct frontal regions (exceptions are Baker et al. 1996; Koechlin et al. 1999).

Here, we review the results from neuroimaging studies in the domains of reasoning and episodic memory retrieval, and examine the evidence for a functional distinction within the prefrontal cortex in a rostrocaudal (anterior–posterior) direction. We present analyses of the distribution of stereotaxic coordinates of activation foci reported by neuroimaging studies in the domains of reasoning and episodic

memory retrieval. These analyses were conducted in order to gain evidence as to what psychological processes may be mediated by the frontopolar cortex and, where possible, to reveal differences between task conditions associated with frontopolar and dorsolateral activations.

3.1 Reasoning: Distribution Analysis

The studies used problem solving tasks such as the Tower of London task, the Wisconsin Card Sorting Test, inductive (or probabilistic) reasoning, and the Raven's Progressive Matrices test. The stereotaxic coordinates of the local maxima of activation reported by these studies are displayed on the rendering of a standardized brain in Fig. 3.

Frontopolar activations were observed as consistently as dorsolateral activations for reasoning tasks. Frontopolar activation was reported in eight of ten studies and dorsolateral activation was reported in seven of the ten studies. The studies that observed dorsolateral activation during reasoning also observed frontopolar activation, with two exceptions in which only frontopolar activation was observed (Goel et al. 1997; Osherson et al. 1998). These two studies, however, used rather demanding

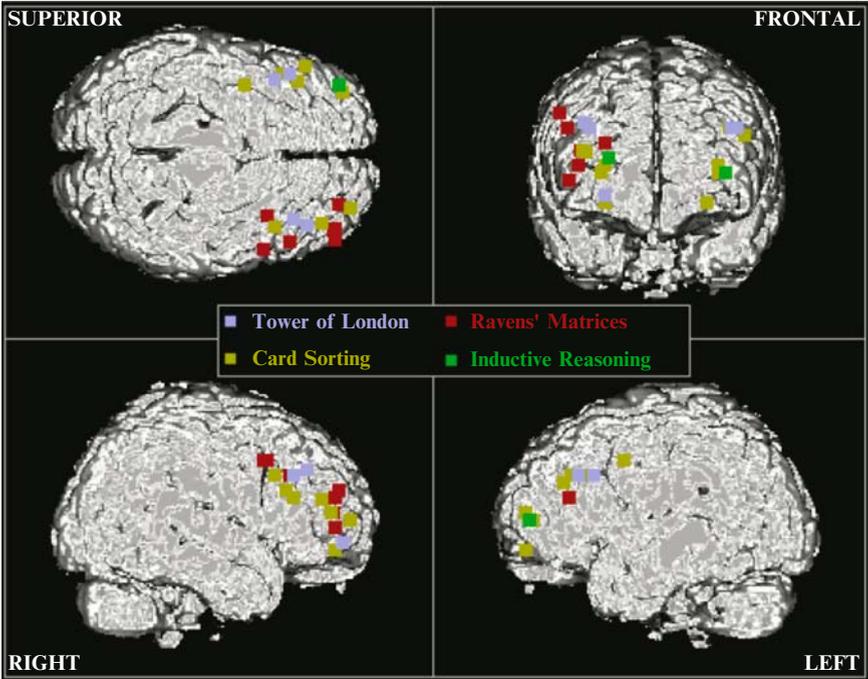


Fig. 3 Activation foci reported during reasoning

baseline conditions that required complex sentence comprehension and semantic decisions. These demanding baselines may have involved dorsolateral activation to the same extent as the reasoning tasks.

3.2 Mental Processes Related to Frontopolar Activation: Evidence from Reasoning Studies

The review of reasoning studies above shows that both dorsolateral and frontopolar areas are frequently activated during reasoning, but it does not distinguish between these two areas. However, a number of researchers have suggested that particular reasoning processes may be of greater significance in recruiting frontopolar activation than others. Baker et al. (1996) proposed that the frontopolar cortex is involved in *sequence selection and evaluation*. Baker et al. used the Tower of London task and compared one condition consisting of “easy” problems that required only two or three moves for an optimal solution and another condition consisting of “difficult” problems that required four or five minimum moves. Even though both types of problems involved planning and evaluation of a sequence of moves, the “difficult” problems required considering a longer sequence of moves than the “easy” problems. The difficult problems were found to produce significantly greater right frontopolar activation than the easy problems, although bilateral increases in dorsolateral activation were also observed. On the basis of evidence from previous studies, Baker et al. attributed the increases in dorsolateral activation to the increased working memory requirements and proposed that the frontopolar activation was reflecting the increased need for sequence selection and evaluation.

There is also evidence to suggest the frontopolar cortex may be involved in *feedback evaluation*. Feedback evaluation is a crucial component of the Wisconsin Card Sorting Task and four of the five studies using a card sorting task reported activation in this region. Tasks other than the Wisconsin Card Sorting Test have also provided support for the idea that the frontopolar cortex is involved in feedback evaluation. Elliott et al. (1997) presented participants with a guessing task based on the formal structure of the Tower of London task and varied whether or not participants received feedback after each response. There was frontopolar activation for the feedback condition relative to the no-feedback condition. No dorsolateral activation was found for this comparison.

Another mental process associated with frontopolar activation is *hypothesis generation and evaluation* – an important aspect of both card sorting and inductive reasoning tasks. During card sorting, participants have to generate hypotheses as to what is the correct sorting rule, and evaluate these hypotheses in light of the feedback.

Inductive reasoning, on the other hand, is in itself considered a form of hypothesis generation and testing (Goel et al. 1997). It has been studied in both the verbal and the visuospatial domain. Neuroimaging studies of verbal inductive reasoning have

operationalized induction as the process of evaluating an argument's plausibility, given certain premises. In this case, a hypothesis about the argument's plausibility would have to be generated and evaluated in light of the information contained in the premises. Inductive reasoning has also been studied through nonverbal tasks, tasks such as the Raven's Progressive Matrices, where the same processes of hypothesis generation and evaluation need to be carried out in the visuospatial instead of the verbal domain. Frontopolar activation was observed during performance of the Raven's Progressive Matrices task across two types of problems (Prabhakaran et al. 1997). This further supports the possibility that this cortical region may be involved when hypotheses are being generated or evaluated.

In summary, there are several mental operations that seem to be associated with frontopolar activation, namely, sequence selection and evaluation, feedback evaluation, and hypothesis generation and evaluation. These mental operations seem to share a common feature that can be described as *evaluation of a self-generated response or plan for action*. This can be a self-generated sequence of moves or a plan for it in the Tower of London task; a self-generated response according to a sorting category in the Wisconsin Card Sorting Test, or a self-generated hypothesis as to the plausibility of an argument or the item which should follow next in the sequence in the case of inductive reasoning and the Raven's Progressive Matrices test. It is possible therefore that the frontopolar cortex is specifically involved in *self-generated evaluation*, a process that is critical when nonroutine cognitive strategies have to be generated and selected in the context of novel tasks or activities.

If self-referential evaluation and introspective thought in general are processes that characterize the role of the frontopolar cortex, this cortical region should play an important role not only in reasoning, but also in other cognitive domains requiring introspectively based decisions.

3.3 Frontopolar Activations in Tasks Other Than Reasoning

Apart from reasoning, activation of the frontopolar cortex has been observed in a number of functional imaging studies employing various cognitive paradigms, such as self-ordered tasks (Owen et al. 1996; Petrides et al. 1993), semantic monitoring tasks (MacLeod et al. 1998), self-relevant tasks (Stone et al. 1998), cognitive branching tasks (Koechlin et al. 1999), and working memory tasks (Cohen et al. 1994; Grasby et al. 1993; Jonides et al. 1997; Rypma et al. 1999; Smith et al. 1996). As a more detailed examination reveals, it is likely that these tasks, under the conditions in which they were presented, involved some form of self-referential evaluation. Self-ordered tasks usually involve a sequence of responses, where each response can be executed only after the previously executed responses are taken into consideration. Petrides et al. (1993) used a task that required participants to say aloud in random order the numbers one through ten without repeating themselves; this produced activation in left frontopolar cortex ($x, y, z = -35, 42, 22$; BA10/46).

Owen et al. (1996) used another self-ordered task that produced activation in the right frontopolar cortex ($x, y, z = 34, 51, 6$; BA10). In this case participants touched eight or 12 circles in a random sequence until one of them changed color. In each trial, participants had to avoid the circles which had changed their color in previous trials. Both tasks seem to require that participants evaluate each response in light of the previous responses that they themselves have previously executed.

Semantic monitoring tasks, on the other hand, should not necessarily require self-referential evaluation. However, the specific task used by MacLeod et al. (1998) required not only classifying individual words according to a prespecified semantic category, but also monitoring the frequency of words that belonged to this category and making an estimate of this frequency for each block. When this conjoint semantic monitoring and target frequency estimation condition was compared with a passive word viewing control task, right frontopolar cortex was found to be activated ($x, y, z = 25, 61, 6$; BA10). In three of the five conditions employed by MacLeod et al., participants had to give a gross estimate (i.e., a percentage) of the target frequency, which makes the task bear a striking resemblance to the previously described inductive reasoning tasks where a hypothesis about the probability of a statement has to be formulated and evaluated. Indeed, relative frequency is considered to be the principal source of information about probability (Gigerenzer and Murray 1987). Therefore, it is possible that the generation and evaluation of a target frequency estimate, rather than semantic classification, was the mental operation responsible for frontopolar cortex activation.

Yet another process, that of cognitive branching, was interpreted as responsible for the bilateral frontopolar activation ($x, y, z = 36, 66, 21$; BA10; and $x, y, z = -36, 57, 9$; BA10) reported by Koechlin et al. (1999). Cognitive branching refers to the process of allocating attentional resources when attention has to be alternated between two concurrently ongoing activities. The cognitive branching condition employed by Koechlin et al. consisted of presenting participants with alternating blocks of uppercase and lowercase letters. As uppercase and lowercase blocks alternated, participants had to alternate between two different sets of goals, making a judgment for each letter presented. During a lowercase block, the judgment for the first letter in the block was whether or not it was “t,” and for subsequent letters in the block whether the current letter and the one presented prior to it were in immediate succession in the word “tablet.” On the other hand, during an uppercase block, the judgment for the first letter was whether or not it was the same as the last letter in the previously presented uppercase block. For subsequently presented letters in uppercase blocks, the judgment was identical to the one for lowercase blocks – whether or not the two letters were in immediate succession in the word “tablet.” Thus, in order to perform the task, participants had to keep in mind the first set of goals while acting on the second, after which they had to shift to keeping in mind the second set, while acting on the first, and so forth. It is difficult to precisely analyze the component processes in such a demanding situation, but it is possible that in a sequence where two sets of goals alternate in a regular fashion such as the one used in this study, keeping track of which set of goals is currently to be followed involves

considering one's own responses to the block of items immediately preceding the current block. Therefore, it is plausible that the task employed by Koechlin et al. involved internally oriented processes.

Another domain in which tasks have sometimes elicited frontopolar activation is working memory. A task that has been used widely in the working memory literature is the *n*-back task, during which participants are presented with a series of items, each appearing one at a time, followed by the next item in the series. The task is to press a button when the item that is being presented at the moment is the same as the one presented a certain number (*n*) of items earlier. For instance, in a 1-back task, a button has to be pressed if the item is the same as the one presented immediately prior to it, whereas in a 2-back task, it has to match the item presented before the last previously presented item, and so on. Using the *n*-back task, Jonides et al. (1997) found right frontopolar activation for a 2-back condition ($x, y, z = -42, 50, 22$; BA10) and bilateral frontopolar activation in a 3-back condition ($x, y, z = -39, 44, 18$; BA10; and $x, y, z = 37, 48, 18$; BA10). Using the same *n*-back task in a 2-back condition, Cohen et al. (1994) observed bilateral frontopolar activation for verbal items such as letters ($x, y, z = -29, 38, 20$; BA10/46; and $x, y, z = 31, 42, 22$; BA10/46), as well as spatial items such as locations ($x, y, z = -26, 49, 11$; BA10; and $x, y, z = 34, 53, 10$; BA10). Similarly, using a 3-back condition, Smith et al. (1996) found left-lateralized frontopolar activation for both letter items ($x, y, z = -37, 55, 2$; BA10) and location items ($x, y, z = -33, 44, 20$; BA10).

Using a different working memory task, Grasby et al. (1993) found bilateral frontopolar activation in a supraspan compared with a subspan condition ($x, y, z = -34, 46, 0$; BA10; and $x, y, z = 24, 52, 0$; BA10). The supraspan condition required the free recall of a list of 15 words immediately after they had been presented, whereas the subspan condition involved free recall of lists of five words. Yet another working memory task, based on a simultaneous item-recognition task developed by Sternberg (1966), was used in a study by Rypma et al. (1999) and bilateral frontopolar activation was reported for a six-letter condition in comparison with a one-letter condition ($x, y, z = -27, 53, 1$; BA10; and $x, y, z = 25, 53, 1$; BA10).

In general, working memory conditions that activate frontopolar cortex involve maintenance of working memory load approaching or exceeding the average short-term memory span: Tasks such as 2- or 3-back, or keeping in mind 15 words or six unrelated letters, are usually considered to be around or above span limit. One possible explanation is that as the number of maintained items approaches or exceeds this limit, there appears a need to strategically organize the process of maintenance. The observed frontopolar activations could be related to this additional process of maintenance organization, which may involve processing of internally generated information (such as particular groupings of the items into chunks). Another possible explanation is that prefrontal cortex activation, including activation of frontopolar cortex, is observed whenever there is increase in task difficulty. The issue of task difficulty and its relation to frontopolar activation will be discussed in greater detail later in this chapter.

3.4 Rostrocaudal Prefrontal Cortex Differences: A Hierarchical Distinction

As mentioned earlier, there is evidence that the dorsolateral prefrontal cortex is specifically involved during the processes of manipulation and monitoring of information within working memory. It represents the second stage of processing in the two-stage model of working memory proposed by Petrides (1994), Petrides et al. (1995) and Owen et al. (1996) and confirmed by more recent neuroimaging findings (D'Esposito et al. 1998).

However, many tasks involving manipulation and monitoring have been shown to produce activation not only in the dorsolateral, but also in the frontopolar cortex. This suggests that the frontopolar cortex may also be involved during these processes. It is, however, possible that as suggested previously these two areas of the cortex are involved in *different types* of manipulation and monitoring. The type of monitoring and manipulation within working memory associated with dorsolateral prefrontal cortex activation has, in the majority of working memory studies, involved monitoring and manipulation of *externally generated* information, such as letters or locations. On the other hand, the evidence that the frontopolar cortex is specifically involved in the process of evaluation of self-generated responses or plans for action suggests that the frontopolar cortex may be needed in addition to the dorsolateral cortex, when the task requires monitoring and manipulation of information that has been internally generated. In this sense, the frontopolar region can be viewed as subserving an additional, third level of executive processing within the human prefrontal cortex (Fig. 4). Therefore, we hypothesize a rostrocaudal distinction within the prefrontal cortex, involving the dorsolateral and frontopolar prefrontal regions, and distinguishing between active processing performed upon information that has been externally generated and processing performed upon information that has been self-generated (Fig. 4, stages II and III). This distinction is hierarchical in both anatomical and functional terms: The dorsolateral prefrontal cortex may be sufficient for the processing of externally generated information, but both frontopolar cortex and dorsolateral cortex are needed when self-generated information is being processed.

3.5 Episodic Retrieval: Distribution Analysis

In an attempt to examine the generality of rostrocaudal prefrontal cortex differences, we next turn to functional neuroimaging results reported in episodic memory retrieval. Episodic retrieval studies have revealed consistent activations in both frontopolar and dorsolateral prefrontal cortex, but they have failed to discover what distinguishes activations in these two prefrontal regions (Wagner et al. 1998; Henson et al. 1999). Nonetheless, the frontopolar and the dorsolateral cortex may subserve distinct functions during episodic retrieval and there is some evidence as to what

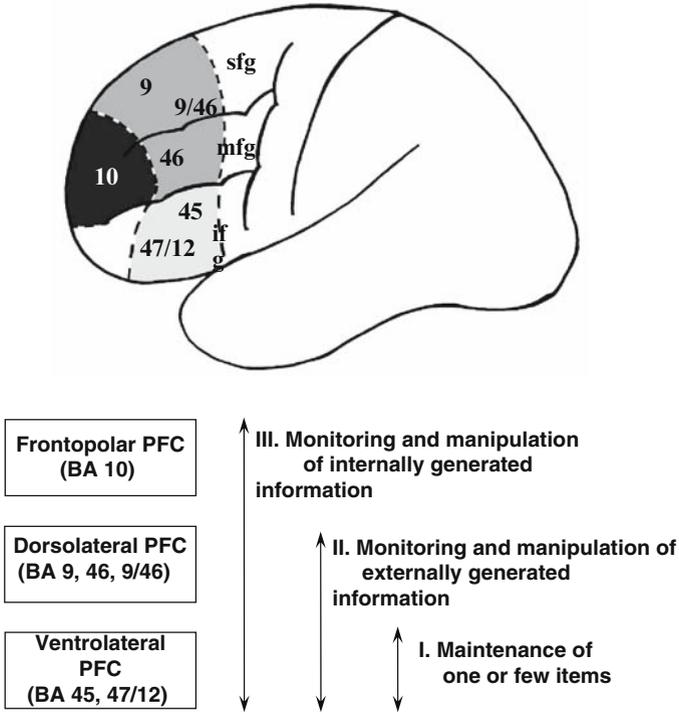


Fig. 4 Hierarchical organization of prefrontal function: a three-stage model. *BA* Brodmann area; *PFC* prefrontal cortex

these functions may be: Activation in the dorsolateral prefrontal cortex has been found to be specifically associated with monitoring processes during episodic retrieval (Henson et al. 1999; Shallice et al. 1994); the role of the frontopolar cortex has been somewhat more controversial but, importantly, one of the leading hypotheses has been that it is associated with a postretrieval evaluation of the self-generated products of the retrieval process (Johnson et al. 1996; Shallice et al. 1994).

The studies in the following review were classified according to the type of episodic retrieval procedure they used. Episodic retrieval tests can be divided into two groups according to the degree to which the memory judgment requires evaluation of self-generated information. We expected that, on the average, tests in which participants have to evaluate self-generated information would be more likely to have resulted in frontopolar activation than when no such introspectively directed evaluation was required.

Tests classified as requiring minimal evaluation of self-generated information included simple episodic recognition procedures, either forced-choice or yes–no recognition. Forced-choice recognition involves indicating which one of two simultaneously presented items (one old and one new) has been previously presented during the acquisition phase; yes–no recognition involves sequential categorization

of individual test items as either old or new. In both cases, successful performance in recognition tests is based on evaluating externally generated information – whether an item has been presented previously or not. It should be noted, however, that even though evaluating self-generated information was not required by the tasks in this group, the possibility that it can occasionally occur cannot be excluded. Indeed, this possibility is especially marked in the sequential yes–no recognition procedure, which may involve setting a criterion for evaluating memory characteristics evoked by test items, which would in its own turn require retrieval and evaluation of previous self-generated responses (Nolde et al. 1998). However, regardless of the possibility that it can occasionally occur, the evaluation of self-generated information is minimally required by these test procedures.

On the other hand, tests classified as requiring more evaluation of self-generated information included cued recall, free recall, and complex recognition procedures such as counting of oddball items within a block. None of these tests can be performed by evaluating externally generated information. In all cases, people must evaluate the information they have generated (or retrieved) themselves in response to some sort of cue or instruction. Cued recall typically involves not only the generation, but also the evaluation of self-generated answers (Nolde et al. 1998). During cued recall, participants are presented with cues to help them remember specific items learned during acquisition. According to the type of cued recall used, these cues can be word stems, word fragments, or one of a pair of associated words (word associates). Participants need to recall the acquisition word with which the stem or fragment can be completed, or which was associated with the word presented as a cue. Typically, each of the cues can be associated with not only studied but also nonstudied words, and therefore participants may generate more than one solution before attributing one to the acquisition task (Nolde et al. 1998). Thus, cued recall appears to require evaluation of information generated by the participants themselves. Similarly, free recall tasks are generally thought to require self-initiated cueing and selection among possible candidate responses, and would also be likely to involve evaluation of self-generated information. Counting the number of oddball items within a block, on the other hand, even though formally classified as a recognition procedure, presents participants with the dual task of having to categorize each item *and* keep track of the number of items in the oddball category. This type of procedure most likely requires some complex cognitive processes similar to those previously discussed for cognitive branching and probability estimation, and is therefore likely to involve evaluation of self-generated information.

The maxima reported by studies included in each of the two groups are plotted onto a rendering of a standardized brain in Fig. 5. While only half of the recognition studies (five out of ten) reported frontopolar activation, nearly all of the other studies (13 out of 15) reported significant activation foci in this region of the cortex. Seven of the ten recognition studies and 11 of the other 15 studies revealed dorsolateral activation.

The results suggest a hierarchical distinction between the dorsolateral and the frontopolar cortex: The dorsolateral cortex appears to be involved in both types of evaluative processes, whereas the frontopolar cortex is activated much more consistently by tasks requiring evaluation of self-generated information.

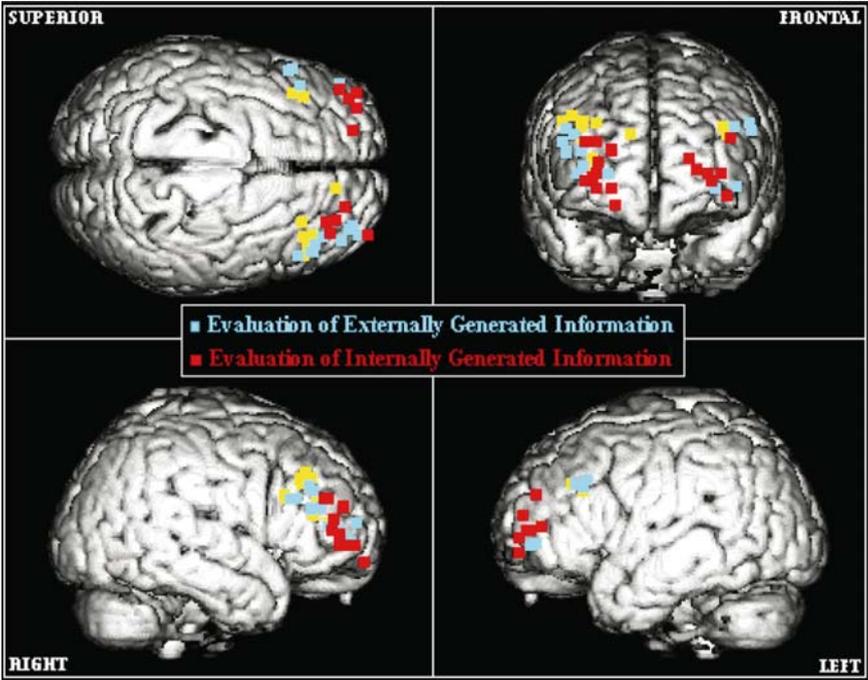


Fig. 5 Activation foci reported during episodic memory retrieval

The review of reasoning, episodic retrieval, and other studies presented here provides evidence that the frontopolar cortex may be specifically involved in complex cognitive activities that require evaluation of self-generated information. Frontopolar cortex is nearly ubiquitously activated by complex reasoning tasks, and the few exceptions may be interpreted in terms of specific experimental details. All complex reasoning tasks demand the evaluation of self-generated information. The review of episodic retrieval studies suggested that retrieval tests which require only evaluation of externally generated information are not likely to activate the frontopolar cortex, whereas tasks that pose an additional requirement for evaluation of self-generated information almost invariably produce activation in this region. This provides further evidence for a hierarchical distinction between the frontopolar region and the more posteriorly located dorsolateral prefrontal cortex. Both types of evaluation are likely to produce dorsolateral prefrontal cortex activation. Therefore, the proposed rostrocaudal prefrontal cortex distinction should not be taken to imply a double dissociation. Instead, it should be taken to suggest a hierarchical organization in which the frontopolar cortex is necessary, although not sufficient, in order for the most complex stages of processing to be carried out (Fig. 4). Thus, not only the frontopolar cortex but also the dorsolateral cortex (and probably other posterior regions) would be needed for the evaluation of self-generated information. Such hierarchical models of information processing are common in sensory and motor systems. Here, we propose such a hierarchical model for prefrontal mediation of thought.

3.6 Lesion Studies and Deficits in Self-Referential Evaluation

Patients with frontal-lobe lesions are often impaired in the tasks discussed previously involving self-referential evaluation. Frontal-lobe lesion patients exhibit deficits in all of the previously reviewed reasoning tasks, including the Tower of London task (Norman and Shallice 1986; Owen et al. 1990; Shallice 1982), the Wisconsin Card Sorting Test (Milner 1963, 1964; Robinson et al. 1980), and inductive inference tasks such as judging frequencies (Milner et al. 1985; Smith and Milner 1988) and cognitive estimation (Shallice and Evans 1978; Vilkki and Holst 1991). Importantly, these studies have included frontal lesions that in many cases involved the frontopolar area. Other findings suggesting impaired self-evaluation after frontal-lobe damage abound, including the lack of behavioral restraint frequently observed after frontal-lobe damage (Miller 1985), increased impulsivity (Miller 1992), utilization behavior (Shallice et al. 1989), and inability to monitor the effectiveness of self-generated plans (Luria 1973). All of these different impairments can be attributed to a general deficit in evaluating self-generated information.

In addition to reasoning, frontal-lobe abnormality seems to be associated with a specific pattern of memory dysfunction. Importantly, there is impairment in memory performance on free recall tests (della Rocchetta 1986; Janowsky et al. 1989; Jetter et al. 1986), although when the same material is tested in recognition procedures performance is relatively preserved (Stuss et al. 1994; for a review, see Wheeler et al. 1995). Free recall was classified in the previous section as likely to require evaluation of self-generated retrieval strategies and retrieval outcomes. Consistent with this, the deficit on free recall in patients with frontal-lobe lesions is generally interpreted as impairment in the subjective organization that aids recall (Gershberg and Shimamura 1995). One instantiation of this free recall impairment is the frequently observed confabulation and faulty retrieval of remote memories in patients with frontal-lobe damage (Baddeley and Wilson 1986; Moscovitch 1989; Stuss et al. 1978; Stuss and Benson 1986). Confabulation is also interpreted as a deficit in retrieval strategy and the evaluation of the search outcome (Baddeley and Wilson 1986, 1988; Burgess and Shallice 1996; Moscovitch 1989; Squire and Cohen 1982). In addition, the performance of patients with lesions in the prefrontal region is also impaired in the previously discussed self-ordered working memory tasks (Milner et al. 1985; Petrides and Milner 1982), for which the ability to generate and evaluate self-generated strategies is critical.

In addition, patients with frontal-lobe lesions exhibit a specific and limited deficit in some particular episodic memory tests such as source memory (Janowsky et al. 1989) and recency judgments (Milner et al. 1991) where, similarly to free recall, self-generated memories must be evaluated, manipulated, or transformed. Patients with frontal-lobe lesions also exhibit a propensity to make false alarms or, in other words, to endorse foil or baseline items as having been seen before (Schacter et al. 1996). This may be related to the previously mentioned processes of criterion setting and could be interpreted as a failure to evaluate and adjust the self-generated criterion used to distinguish between studied items and other items that bear similarity to the studied items.

Unfortunately, in the majority of clinical cases there is a lack of detailed knowledge about the lesions, and even when their extent is known, it rarely follows precisely functional or architectonic borders. This, in addition to the need to average across patients with sometimes very different lesion locations, can greatly reduce the ability to make subregional inferences. However, at least one lesion study has provided evidence consistent with the rostrocaudal prefrontal distinction proposed here. Vilkki and Holst (1991) used a digit symbol test to assess the ability to achieve a self-selected goal defined as the number of symbols the patients estimated would be achieved in 1 min or less. Patients with anterior prefrontal lesions were found to be more impaired than patients with posterior prefrontal lesions in estimating achievable goals – a process relying extensively on self-referential evaluation.

3.7 Relation Between Neuroimaging and Patient Findings

The following parallel can be drawn between the brain lesion and functional neuroimaging results discussed so far: Patients with lesions in the prefrontal region appear to be impaired in tasks, such as free recall, that are usually associated with frontopolar activation (in addition to dorsolateral activation). On the other hand, they exhibit only mild or no impairment in tasks such as recognition, that tend to produce dorsolateral (but no frontopolar) activation in healthy controls. This may at first appear somewhat surprising because it seems as if the dorsolateral cortex is not necessary for performance in neuropsychology studies of brain-lesioned patients, even though it is consistently recruited by the same tasks in neuroimaging studies of healthy people. In principle, there is a possibility that at least some of the activation observed in neuroimaging studies is epiphenomenal and that damage to a consistently activated region may have little or no effect on performance. There are, however, at least two other possible explanations, consistent with a hierarchical rostrocaudal prefrontal organization. First, for statistical reasons, a group of mixed prefrontal lesions is likely to include more patients with lesions in either one of these two regions than patients with lesions in only one of them – the dorsolateral region. For tasks requiring both regions, lesions extending over either of the two regions would produce deficits, whereas for tasks requiring only dorsolateral cortex, only a subset of these lesions – the ones extending over the dorsolateral region – would produce deficits. Therefore, on average, the group would show a stronger deficit for tasks requiring both regions than for tasks requiring only dorsolateral cortex.

This alone, however, may not be sufficient to account for the normal performance of prefrontal groups in tasks that involve dorsolateral activation. In view of the hierarchical relationship between the two regions, it is conceivable that task processes usually associated specifically with dorsolateral prefrontal cortex activation may also be subserved by the frontopolar cortex, which, although normally not recruited, may take over some of the functions of the dorsolateral prefrontal cortex when the latter is lesioned. In such a case, only the patients with lesions extending over both the dorsolateral cortex and the frontopolar cortex would be impaired, which would

greatly reduce the probability that the group on the average will exhibit a deficit. However, whether the frontopolar cortex in patients with dorsolateral lesions can indeed assume functions typically subserved by the dorsolateral cortex remains to be determined by future neuroimaging studies of patient populations. In any case, it is striking that the deficits seen in patients with frontal lesions are more closely linked to frontopolar than dorsolateral activations in healthy people.

3.8 Conclusions

The review of reasoning and episodic retrieval studies presented here suggests that the frontopolar cortex is a functionally distinct prefrontal region that may be selectively involved in active processing, such as evaluation, monitoring, or manipulation, performed upon internally generated information. It is proposed that there may be a hierarchical distinction in a rostrocaudal direction between the frontopolar and the dorsolateral prefrontal regions of the cortex. Dorsolateral cortex may be sufficient for the evaluation or manipulation of externally generated information, whereas frontopolar cortex is additionally required when evaluation and manipulation of internally generated information needs to be performed. Such a hierarchical distinction is consistent with, and can be viewed as an extension of, the two-stage model of processing within the lateral prefrontal cortex, which has been previously proposed in the literature. This latter model has viewed the ventrolateral and dorsolateral regions as subserving two different stages of executive processing within the lateral prefrontal cortex, with the dorsolateral region being involved at the second stage, where monitoring and manipulation of information held in working memory is required. The rostrocaudal prefrontal cortex distinction proposed here goes one step further and suggests that the frontopolar region in the human prefrontal cortex can be seen as subserving a third stage of executive processing, involving evaluation of information that has been generated at the previous stage of executive processing. Thus, the ventrolateral, dorsolateral, and frontopolar regions can be seen as forming a three-stage hierarchical system within the prefrontal cortex.

4 Evaluating Self-Generated Information and Introspective Thought

To test the hypothesis that the frontopolar cortex is involved in the evaluation of self-generated information, we performed an event-related fMRI experiment, using a simple matching task designed to contrast directly the processing of internally and externally generated information (Fig. 6). The internal (Fig. 6, regions A, B) and external (Fig. 6, regions C, D) task conditions were similar in terms of overall demands, but differed in the critical requirement for processing self-generated information. During the sample phase, two objects were presented in the top part of

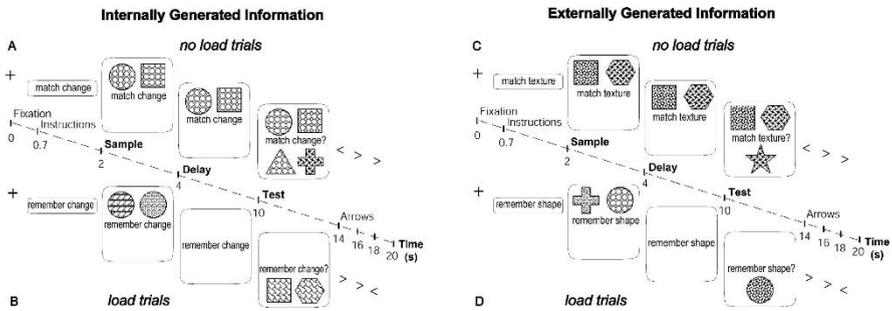


Fig. 6 Behavioral task. Stimuli were objects of six possible geometric shapes, filled with one of six possible textures. Each trial started with a fixation cross, followed by an instruction cue. During the sample phase, a target set of two objects was presented at the upper part of the screen for 2 s. This was followed by a 6 s delay phase, during which the target set either remained on the screen (no-load trials) or was removed (load trials). During the test phase, a probe set of one or two objects was presented at the bottom half of the screen and subjects had to match it to the target set according to the instructions. On internally generated information trials (**A**, **B**) subjects had to infer the dimension of change between the top two objects (shape or texture) and decide whether the bottom two objects also change along this dimension. On externally generated information trials (**C**, **D**) subjects had to decide whether the bottom object matched any of the top objects along a specified dimension (shape or texture). On no-load trials (**A**, **C**) all objects were available on the screen during the decision, while on load trials (**B**, **D**), only the bottom set of objects was present and matching had to be performed from memory. Subjects responded with a “yes” or “no”, by pressing one of two buttons on a hand-held button box. The probe remained on the screen until the subject’s response, but no longer than 2 s. During the 8 s baseline period at the end of each trial, an arrow appeared at the center of the screen every 2 s, pointing randomly to the right or to the left. Subjects had to respond within 500 ms by pressing a key corresponding to the arrow’s direction

the screen. In the internal condition, subjects had to infer the dimension of change between the objects (shape or texture), whereas in external trials, they had to encode the objects in terms of their perceptual features. During the delay phase, the sample objects either remained on the screen (no-load trials) or were removed from the screen (load trials). In the latter case, subjects had to retain the relevant information in working memory. During the test phase one or two match stimuli were presented. In internal trials, subjects had to infer the dimension of change between the bottom-two objects and decide whether it matched the previously inferred dimension of change between the top objects. In external trials, subjects had to decide whether the bottom object matched any of the top objects along a specified dimension (shape or texture). Thus, the test phase of each trial required evaluating either externally generated information about objects’ features, or internally generated information about the dimension of change between objects’ features. The contrast between the test phases of internal and external trials was designed to identify brain regions preferentially involved in evaluating internally generated information.

Half of the trials (Fig. 6, regions A, C) posed no maintenance requirement, while the other half (Fig. 6, regions B, D) required maintenance of relevant information about the sample set in working memory. The purpose of this load manipulation was twofold: first, to examine the processes of generation and maintenance of

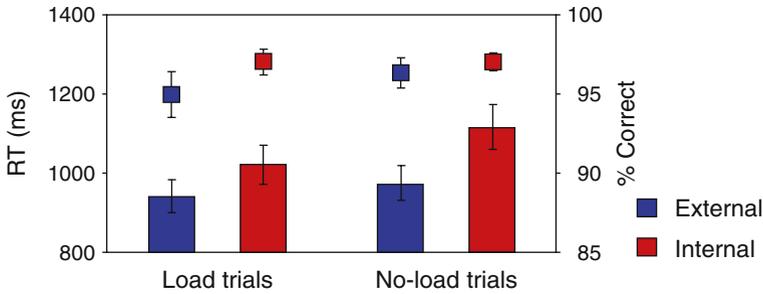


Fig. 7 Behavioral performance. Bars show mean reaction times across conditions and symbols show mean accuracy. Error bars indicate standard error of the mean. See Results and Discussion sections for details

self-generated information (occurring during the sample and delay phase of load trials, respectively), and second, to assess the contrast between evaluating different types of information in the absence and presence of concurrent maintenance requirements (occurring during the test phase of no-load and load trials, respectively).

Behavioral results showed that subjects maintained a high level of performance throughout the experiment (Fig. 7). The mean accuracy was 96.34% (standard error 0.73%) and did not differ significantly across conditions. Responses occurred on the average 1,014 ms (standard error 45.96 ms) after the onset of the test stimulus, and were 114 ms slower during internal trials than during external trials ($F_{1,11} = 34.8, p < 0.001$) and 62 ms slower during no-load trials than during load trials ($F_{1,11} = 24.5, p < 0.005$).

A whole-brain voxel-based analysis contrasting the evaluation of internally and externally generated information (Fig. 8b) yielded only three areas of activation: bilateral rostrolateral prefrontal cortex (strongly on the right, weakly on the left) and left primary visual cortex (presumably owing to the different number of objects that had to be visually inspected). Rostrolateral prefrontal cortex activation was located within the predicted region (Fig. 8a), anatomically defined (Christoff et al. 2001) as the region of intersection between middle frontal gyrus and BA10.

These findings were confirmed by an independent region-of-interest analysis of the event-related signal in rostrolateral prefrontal cortex during the test phase (Fig. 8c,d, yellow panels). Rostrolateral prefrontal cortex signal increased during evaluation of internally compared with externally generated information both during no-load ($F_{1,11} = 7.49, p < 0.05$) and during load ($F_{1,11} = 5.29, p < 0.05$) trials. Furthermore, this differential recruitment was specific to the process of evaluation, and was not observed during generation ($F_{1,11} = 1.96, p = 0.19$) or maintenance ($F_{1,11} = 0, p = 0.98$) of internally generated information (Fig. 8c, gray panels) – a result also supported by a significant phase by condition interaction ($F_{2,22} = 6.53, p < 0.01$). These results indicate that the rostrolateral prefrontal cortex is preferentially recruited during deliberate, evaluative processing performed upon internally generated information, independent of concurrent maintenance requirements.

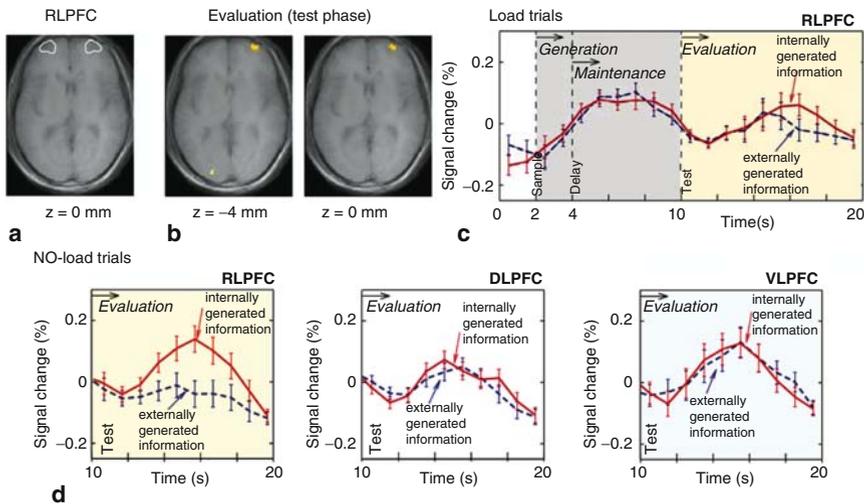


Fig. 8 Anatomical prediction and fMRI results. (A) The hypothesized (Christoff & Gabrieli, 2000) region of activation, RLPFC, anatomically defined (Christoff et al., 2001) as the intersection between middle frontal gyrus and BA10. (B) Results from a whole-brain group analysis: Regions showing significant increase during evaluation of internally generated information relative to the evaluation of externally generated information (load and no-load trials combined). Activations are overlaid on an average anatomical image and are thresholded at $p < 0.05$ corrected for multiple comparisons. (C, D) Event-related responses in anatomically defined regions of interest. Plots show the median across subjects (\pm s.e.) in percent signal change. (C) Time-course observed in right RLPFC during the sample, delay, and test phases of load trials. (D) Time-course observed in right RLPFC, right DLPFC, and right VLPFC during the test phase of no-load trials

To test further the regional specificity of rostralateral prefrontal cortex recruitment, the event-related signals in anatomically defined dorsolateral prefrontal cortex and ventrolateral prefrontal cortex regions were examined during the evaluation of internally and externally generated information (Fig. 8d, blue and green panels). Only no-load trials were included to avoid effects of concurrent memory load, to which these two regions have been shown to be sensitive (D'Esposito et al. 1998; Fuster 1980; Goldman-Rakic 1987; Owen 1997; Petrides 1994). There was no difference in event-related signal between evaluation of internally and externally generated information in either dorsolateral prefrontal cortex ($F_{1,11} = 0.14, p = 0.71$) or ventrolateral prefrontal cortex ($F_{1,11} = 0.15, p = 0.70$). Furthermore, the regional specificity of effect in rostralateral prefrontal cortex (Fig. 8d) was supported by a significant region by condition interaction ($F_{2,22} = 4.61, p < 0.05$). Although the two posterior lateral prefrontal cortex subregions did not respond differentially between the internal and external conditions, both subregions were activated during both conditions, as revealed by the presence of a significant quadratic trend in dorsolateral prefrontal cortex during internal ($T_{94} = 3.36, p < 0.005$) and external ($T_{94} = 3.46, p < 0.001$) trials, and in ventrolateral prefrontal cortex during internal ($T_{94} = 4.02, p < 0.001$) and external ($T_{94} = 4.15, p < 0.001$) trials.

In contrast, rostrolateral prefrontal cortex was recruited only during internal trials ($T_{94} = 4.08, p < 0.001$), but not during external trials ($T_{94} = 0.96, p = 0.34$).

These results provided direct evidence in support of the hypothesis that the rostral region of the human lateral prefrontal cortex is involved in processing self-generated information. The fMRI signal in rostrolateral prefrontal cortex showed a selective increase during processing of internally generated information compared with externally generated information. This increase was specific to the evaluation phase of each trial and was not observed during the generation or maintenance of self-generated information. In contrast to rostrolateral prefrontal cortex, the more posterior dorsolateral prefrontal cortex and ventrolateral prefrontal cortex regions did not differ in activation between the internal and external conditions, but were nevertheless recruited during both conditions. These results are consistent with the hierarchical model of lateral prefrontal cortex organization discussed earlier (Christoff and Gabrieli 2000), according to which dorsolateral prefrontal cortex and ventrolateral prefrontal cortex are involved when externally generated information is evaluated, whereas rostrolateral prefrontal cortex becomes additionally recruited when internally generated information needs to be evaluated.

Such explicit processing of self-generated information may exemplify some of the highest orders of transformation in which the prefrontal cortex engages during the perception–action cycle (Benson 1993; Fuster 1980; Mesulam 1998; Stuss and Benson 1986; Wise et al. 1996). It may also be one of the mental processes that distinguish humans from other primate species. There are profound disparities among different primate species in their natural ability to process internally generated information. This is demonstrated by differences in performance in tasks requiring judgments analogous to that required during the test phase of the internal condition of the task employed here (Fig. 6, region A). Such tasks are often referred to as “relational matching-to-sample” procedures (Premack 1983) and can be distinguished from the traditionally employed “identity matching-to-sample” procedure, in that they require the animal to match abstract information about the relationship between a pair of objects (e.g., “same” or “different”) to the relationship between another pair of objects, irrespective of object identities. Only humans and chimpanzees with a history of language (Premack 1983) or token training (Thompson et al. 1997) can perform tasks requiring such judgments, while monkeys fail even after extensive training (Thompson and Oden 2000). Furthermore, humans spontaneously develop this ability as early as 5 years of age (Halford 1984), while chimpanzees demonstrate it only in adulthood and only after extensive symbol training. This evolution in ability is paralleled by a twofold increase in the relative size of BA10 from chimpanzees to humans (Semendeferi et al. 2001) – an increase that appears to be selective to this region and occurs even though the relative size of the frontal lobe remains the same between the two species (Semendeferi et al. 1997, 2002). Although further anatomical and cytoarchitectonic studies are needed in order to establish with greater detail and certainty the changes BA10 has undergone in the course of primate evolution, this combination of behavioral and neuroanatomical evidence is consistent with the view that BA10 may play a critical role in mental operations that have emerged at the latest stages of evolutionary development.

Finally, the present study demonstrates involvement of lateral BA10 during the evaluation of self-generated cognitive information, whereas other functional neuroimaging studies have shown that medial BA10 is activated during judgments of self-generated emotional states (Damasio 2000; Gusnard et al. 2001; Lane et al. 1997; Zysset et al. 2002). This suggests that the entire region may be involved in the explicit processing of internally generated information, with lateral BA10 recruited during cognitively oriented tasks and medial BA10 recruited during emotionally oriented tasks. This ability to become aware of and explicitly process internal mental states – cognitive as well as emotional – may epitomize human mental abilities and may contribute to the enhanced complexity of thought, action, and social interactions observed in humans.

5 Spontaneous Thought Processes

The study of higher cognitive function has focused almost exclusively upon mental processes occurring during complex, demanding cognitive tasks. The flow of inner mental events, however, continues even when no tasks are present, forming a “stream of thought” in William James’s (1890) classic phrase. Such inner, spontaneous thought processes have been difficult to observe and characterize using traditional experimental methods. Nevertheless, several lines of research from the behavioral literature and a number of functional neuroimaging observations provide relevant implications regarding their cognitive and neural basis. Here, we summarize behavioral and neuroimaging evidence indicating that spontaneous, task-unrelated cognitive processes share common cognitive and neural mechanisms with purposeful, task-related thought processes. This evidence, including a review of the relevant literature and findings from a new fMRI study, suggests that spontaneous thought is based upon higher-order cognitive processes and brain regions, among which long-term memory processes supported by temporal lobe structures may play a particularly prominent role.

A long-established tradition of behavioral research has aimed at studying spontaneous thought processes. Such processes have been referred to as “daydreaming” (Singer 1966; Giambra 1979), “mind-wandering” (Antrobus et al. 1970), “stimulus-independent” (Antrobus 1968; Teasdale et al. 1993) or “task-unrelated” thought (Giambra and Grodsky 1989). Despite apparent differences in terminology, however, the target of research across studies has been the same: thought processes that occur spontaneously and bear no relation to the task at hand.

These behavioral studies have indicated that spontaneous, task-unrelated thought processes are closely linked to the same cognitive mechanisms that underlie deliberate, task-related thought processes. Neuroimaging evidence offers remarkably similar conclusions. Most of this evidence has been derived from *activation findings in higher cortical region in the absence of demanding tasks*.

The absence of task in the context of neuroimaging is typically referred to as “rest” and consists of blocks during which subjects are typically asked to simply

remain lying still in the scanner and “do nothing.” Such rest conditions were originally intended to provide a baseline against which target conditions can be assessed. As Seneca remarked, however, in 62 AD, long before the advent of neuroimaging, “The fact that the body is lying down is no reason for supposing that the mind is at peace. Rest is sometimes far from restful.”¹ If rest is marked by spontaneous thought processes relying on the same cognitive mechanisms as task-related thought, then an overlap in the pattern of brain activation during rest and cognitive tasks should be expected.

Indeed, such an overlap has been observed ever since the beginning of neural explorations of higher cognition. Ingvar (1975) was the first to report a “striking similarity” between the relative distribution of blood flow in the “problem solving mode,” on the one hand, and in the “resting mode,” on the other hand. He observed that the relative increase in blood flow over frontal regions associated with a performance of a reasoning test (the Raven’s Progressive Matrices) was matched, and even surpassed, by frontal increases in the absence of a task. Ingvar (1979) termed this resting pattern “hyperfrontal,” and attributed it to the fact that “thought processes in resting consciousness are constantly active.”

In the time since these early observations, brain imaging techniques have undergone a refinement in spatial and temporal sensitivity. Despite the lessons from the early neuroimaging findings, however, the use of a resting baseline for the study of higher cognitive processes has remained a common practice, frequently justified by the argument that mental processes during rest are likely to be unsystematic and unorganized, so that any corresponding neural activation would be nonlocalized and negligible. On several occasions, however, researchers have presented evidence to the contrary, demonstrating that particular brain regions are systematically activated during rest.

One line of evidence suggesting that particular regions are consistently recruited during rest comes from observations of the *absence* of task-related activation in particular brain regions when a resting baseline is used, indicating that these regions are activated not only during the task, but also during rest. For instance, Kosslyn et al. (1995) observed visual cortex activation during a visual imagery task, but only when it was compared with a listening baseline condition; when a resting baseline was used, imagery activation was obscured, owing to the presence of rest-related activation in visual cortex. A similar pattern of findings was observed for medial temporal lobe structures (Stark and Squire 2001). In this study, brain structures such as the hippocampus and parahippocampal gyrus were activated not only during task-related memory encoding and retrieval, but also during periods of rest (in comparison with several alternative nonresting baseline conditions). The authors argued that “periods of rest are associated with significant cognitive activity,” including incidental encoding and retrieval processes that would account for the observed rest-related activation.

In addition, findings of absence of activation in another brain region, the rostralateral prefrontal cortex, have also been linked to the use of resting baselines

¹ *Letters from a Stoic*, Penguin, p. 111.

(Christoff and Gabrieli 2000). This prefrontal region is consistently activated during higher-order cognitive tasks, such as problem solving (Baker et al. 1996; Christoff et al. 2001) and complex memory retrieval (for a review, see Christoff and Gabrieli 2000). Buckner et al. (1996), however, used such a complex memory retrieval task involving cued recall of paired associates, and observed no rostrolateral prefrontal cortex activation when a resting baseline was used; when a nonresting word repetition baseline was used, however, rostrolateral prefrontal cortex activation was apparent. Similarly, Ragland et al. (1998) observed no rostrolateral prefrontal cortex activation when a problem solving task, the Wisconsin Card Sorting Test, was compared with rest – although such activation has been consistently reported for this task in comparison with nonresting baselines (Berman et al. 1995; Goldberg et al. 1998; Nagahama et al. 1996). Thus, the rostrolateral prefrontal cortex appears to be another brain region consistently recruited during rest – a recruitment that is likely due to evaluative processes directed towards the subjects' own internal cognitive states during the resting period (Christoff and Gabrieli 2000; Christoff et al. 2003).

Instead of focusing on the absence of activation in particular brain regions, some researchers have argued, similarly to Ingvar (1975, 1979), that the overall pattern of brain activation during rest resembles remarkably the pattern of activation associated with particular higher cognitive functions. Andreasen et al. (1995) used an episodic memory task requiring the recall of a specific event from one's past experience, and a rest condition (or "random episodic silent thinking," as they described rest, using an intentionally ironic acronym). Compared with a semantic memory condition consisting of recalling words that start with a specific letter, both the episodic and the rest condition produced activation in higher cortical regions, including prefrontal and parietal association cortices. Andreasen et al. argued that rest is likely to be associated with "random episodic memory" processes, or a type of free-association, uncensored recollection of past experiences. Indeed, in debriefing interviews with subjects after the study, mental activity during rest was described as "quite vigorous" and consisting of a mixture of freely wandering past recollections, future plans, and other personal thoughts and experiences that appeared to be loosely linked.

A related set of findings was reported by Binder et al. (1999), who observed a largely overlapping set of polymodal cortical regions activated both by a semantic retrieval task and by rest. The semantic task required subjects to listen to the names of animals (e.g., squirrel), and to respond when a named animal is found in the USA and is used by people (e.g., cow). Compared with a perceptual baseline (a tones task during which subjects listened to a sequence of low and high tones and had to respond when it included two high tones), both the semantic and the rest condition produced activation in regions similar to those reported by Andreasen et al. (1995) – prefrontal and parietal association cortices, medial temporal lobe, and cingulate cortices. Binder et al. argued that the observed rest-related pattern of activation reflected conceptual processes occurring during the conscious resting state: processes involving semantic knowledge retrieval, representation in awareness, and manipulation of represented knowledge.

This summary of findings shows that a number of higher cortical regions, including visual areas, medial temporal lobe, and lateral association cortical areas, are consistently recruited during rest as well as during a variety of higher cognitive tasks. Furthermore, this recruitment has been associated with specific higher cognitive functions, such as visual imagery, memory retrieval, conceptual processing and problem solving – processes that seem to occur both in the presence and in the absence of cognitive tasks.

5.1 Rest as a Condition of Interest

Discussions of neural recruitment associated with cognitive processes during rest have concentrated either on a particular brain region (Kosslyn et al. 1995; Christoff and Gabrieli 2000; Stark and Squire 2001), or on a network of activations overlapping between rest and a particular cognitive function, such as episodic (Andreasen et al. 1995) or semantic (Binder et al. 1999) retrieval. Furthermore, although the importance of studying the spontaneously occurring cognitive processes during rest has been emphasized repeatedly, virtually all discussion of these processes has been based on comparisons between rest, on the one hand, and some task posing relatively high cognitive demands, on the other hand.

If rest is to be treated as a condition of interest, however, it is necessary to examine the whole-brain pattern of activation resulting from a comparison between rest and a baseline task that poses only minimal cognitive demands and is thus as closely matched to rest as possible. In the next section, we describe an fMRI study (Christoff et al, 2004) in which rest was explicitly treated as a condition of interest, and was compared with a baseline task requiring only minimal cognitive demands, in order to assess the resulting whole-brain pattern of activation.

5.2 Rest Compared with a Task of Minimal Cognitive Demands: An fMRI Study

Subjects alternated between performing an arrows task and resting (Fig. 9). Blocks were 16 s long and there were eight blocks of each condition. During the arrows task, an arrow appeared on the screen every 2 s, pointing randomly to right or left. Subjects responded with their right hand, pressing one of two buttons on a hand-held button-box (right button for right arrow and left button for left arrow). They were instructed to respond as quickly as possible after each arrow's onset, and were told responses would be considered incorrect if they occurred later than 500 ms after the arrow onset.

Behavioral performance indicated that subjects followed closely the arrows task instructions. The mean accuracy was 98% (standard error 0.52%; range across subjects 94–100%), and all responses occurred within 500 ms after the arrow's onset, with a mean response time of 353 ms (standard error 15.92 ms; range across subjects 270–452 ms).

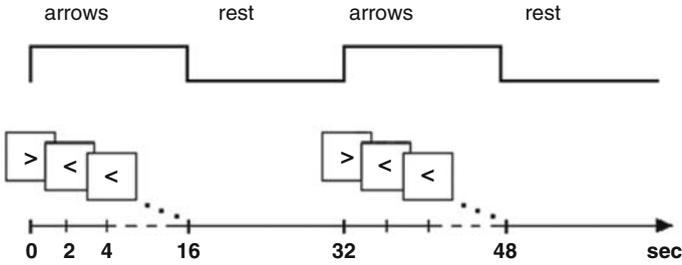


Fig. 9 Behavioural paradigm. Rest was compared to a closely matched, continuously engaging task of minimal cognitive demands (arrows)

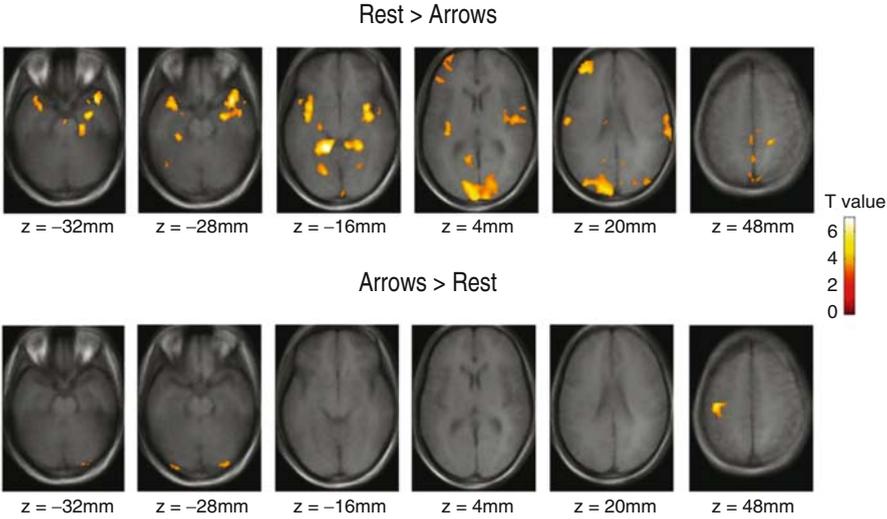


Fig. 10 Activation results. Whole-brain pattern of activation resulting from random-effects group analysis (12 subjects). Activation maps are displayed on axial slices derived from the group-averaged anatomical image. Results are thresholded at $p < 0.005$, with an extent threshold of 10 voxels

Comparing rest and the arrows task yielded activations in multiple regions (Fig. 10). Regions of strong activation in right temporopolar cortex and left parahippocampal gyrus were observed, surviving a threshold of $p < 0.05$ corrected for multiple comparisons throughout the brain. After relaxing the activation threshold to $p < 0.001$ uncorrected, the temporopolar and parahippocampal activations were found to extend bilaterally. At this threshold level, several additional regions of activation were observed, including left rostrolateral prefrontal cortex, primary and extrastriate visual areas, left insula, and right inferior parietal cortex.

Comparing the arrows task and rest yielded a single cluster of activation in the left primary motor cortex (Fig. 10). Activation in this cluster was significant at $p < 0.05$ corrected for multiple comparisons within an a priori defined region of interest comprising the left motor cortex (BA4).

A network of regions related to spontaneous cognitive processes was identified, by treating rest as a condition of interest and comparing it with a continuously engaging task of minimal cognitive demands. The most robust activation was localized in temporal lobe structures, including lateral anterior and medial temporal regions. Activations were also observed in anterior lateral prefrontal cortex and visual cortex areas. Thus, neural recruitment during rest was statistically robust and consistently localized to specific brain regions. Furthermore, the strength of observed activations was comparable to that seen during many highly demanding cognitive tasks.

The observed activations were localized to brain regions that have been implicated repeatedly in a variety of higher cognitive functions – as well as rest (Andreasen et al. 1995; Binder et al. 1999). However, unlike previous related studies, no cognitive task was present in either condition of the present comparison; therefore, the observed pattern could not have been influenced by a relative difference in the employment of particular task-related cognitive processes. Furthermore, cognitive demands posed by the two conditions in the present comparison were kept at a minimum; thus, the activation pattern was also unlikely to be influenced by variations in cognitive demands. The lack of modulation in medial prefrontal cortex – a region frequently activated with reduction in cognitive demands (Shulman et al. 1997; Raichle 1998; Mazoyer et al. 2001) – was, therefore, likely due to the lack of modulation of cognitive demands in the present comparison.

6 Final Conclusions

Neuroimaging and patient studies such as those outlined here bring us closer to understanding the complex processes underlying human thought and reasoning. The proposed anterior-to-posterior hierarchical organization of thought within the lateral prefrontal cortex hints at the importance of considering this region in terms of functionally distinct subregions. In particular, the apparent organization of the lateral prefrontal cortex according to different levels of abstraction in thought, with more abstract thought distributed in the anterior direction, has potential implications for cognitive models of cognition and thought as well as for neuropsychological investigations of executive function. Nevertheless, full understanding of human thought will not be achieved until the complete organization and functional connections of the lateral prefrontal cortex are understood, including both local interconnections within the lateral prefrontal cortex, as well as its long-range connections with other cortical regions, including the temporal lobe and the basal ganglia. Future research aimed at further elucidating the functions and interactions of these regions will create a clearer picture of the brain mechanisms involved in human cognition. However, this picture will remain incomplete unless light is shed on spontaneously occurring, undirected thought processes and phenomena, including mind-wandering and insight during problem solving, as well as on goal-directed thought processes. Understanding our own thought processes from a scientific and cognitive neuroscience perspective is a daunting and challenging task, which may never be fully

achievable. In our striving to achieve understanding, we may change those very thought processes which we are trying to understand. But possibly precisely because of this, achieving such an understanding remains one of the most important goals of contemporary neuroscience.

Acknowledgements Preparation of this chapter was supported by a Tula Foundation Young Scientist award and a Canadian Foundation for Innovation (CFI) award to K.C. I am indebted to Rachelle Smith for her exceptional help and thoughtful comments and suggestions in preparing this chapter.

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