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Article

2003

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How to cite

ZYSSET, Stefan et al. Functional specialization within the anterior medial prefrontal cortex: a functional magnetic resonance imaging study with human subjects. In: Neuroscience Letters, 2003, vol. 335, n° 3, p. 183–186. doi: 10.1016/S0304-3940(02)01196-5

This publication URL: <https://archive-ouverte.unige.ch/unige:98094>

Publication DOI: [10.1016/S0304-3940\(02\)01196-5](https://doi.org/10.1016/S0304-3940(02)01196-5)

Functional specialization within the anterior medial prefrontal cortex: a functional magnetic resonance imaging study with human subjects

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Received 20 August 2002; received in revised form 10 October 2002; accepted 10 October 2002

Abstract

This study investigated the functional neuroanatomy of the anterior medial prefrontal cortex (aMPFC). Previous studies have shown that the aMPFC is involved in evaluative judgment and self-referential processes. Specifically, different sections of the aMPFC are differentially influenced by attention demanding processes. Whereas the dorsal section is supposed to be involved in self-referential processes, the ventral section is assumed to be attenuated during attention demanding processes. The present study investigates the involvement of the dorsal and ventral aMPFC in evaluative judgment by using functional magnetic resonance imaging with spin-echo echo-planar-imaging. Processes involved in evaluative judgment are attention-demanding, self-referential and activate regions in the dorsal and ventral section of the aMPFC. Attention demanding tasks do not necessarily lead to an attenuation of the ventral section of the aMPFC, a region mainly involved in emotional and affective processing.

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Keywords: Fronto-medial cortex; Evaluative judgment; Self-referential processes; Functional magnetic resonance imaging; Spin-echo echo-planar-imaging; Attention-demanding processes

The anterior medial prefrontal cortex (aMPFC) has been in the focus of attention of neuroscience over the last few years. The dorsal aMPFC cortex includes the medial part of Brodman Area (BA) 9m/10m(32). The ventral portion of aMPFC includes the pre- and subgenual parts of BA10/32/14 [16]. aMPFC activations have been reported in the context of 'theory of mind' [8], evaluative judgment [20], self-referential processes [9], self-initiated thoughts [14], coherence processes [6], or processing of intentions [3]. The ventral aMPFC (Fig. 2) appears to play an essential role in anticipatory behavior [1]. Further, the aMPFC appears to be part of a network integrating cognitive task performance and emotion [2,4,18]. This is further supported by the common finding that blood flow in the aMPFC is said to be decreased during emotionally neutral but attentionally demanding cognitive tasks [17]. Gusnard et al. [9] put forward that the dorsal and ventral aMPFC are differentially influenced by attention demanding tasks and explicitly self-

referential tasks. Self-referential mental processes appear to be associated with increases in blood flow in the dorsal aMPFC, whereas emotional and affective processing [2] tend to be attenuated in the ventral aMPFC during attention-demanding tasks. More generally, we argue that the aMPFC mediates meta-control processes [11], which resolve conflicts between subprocesses and incorporate different aspects of internal and external events.

In a previous functional magnetic resonance imaging (fMRI) experiment we were able to show that the aMPFC (BA 9m/10m), along with the inferior precuneus and the inferior frontal gyrus, plays an essential role in evaluative judgment [20]. In contrast to semantic judgments (George Bush is president: yes/no), evaluative judgments (George Bush is a good president: yes/no) are a special type of judgment, in which the internal scale is related to the person's internal value system. This situation can be considered as incompletely specified, the response is not evident and an involvement of the ventral aMPFC would be expected [5].

However, the measurement of ventral aMPFC with fMRI using gradient-echo echo-planar-imaging (GE-EPI) at 3

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Tesla is problematic, as this region is especially prone to signal voids caused by susceptibility artifacts [15]. The previous study [20] and most other fMRI studies use GE-EPI, so that the detection of activations in the ventral section of the aMPFC cannot be guaranteed. Most studies reporting orbito-frontal or ventral aMPFC activations are PET studies. For this reason we re-ran the above-mentioned experiment using spin-echo (SE)-EPI for image acquisition in order to find out whether the activation extends all along the aMPFC. SE-EPI has the advantage over conventional GE-EPI that signal losses caused by strong susceptibility gradients are not present and signal voids will be eliminated [15]. SE-EPI at 3T is sufficiently sensitive to be used in cognitive studies, albeit with a reduction in z-scores of about a factor of three [15].

Eighteen healthy subjects (right handed, 20–31 years of age, 11 female) were tested using fMRI with SE-EPI. All subjects gave written informed consent prior to scanning.

Eighty semantic items, 80 evaluative items, 40 baseline trials ('press left button' or 'press right button'), and 40 empty trials were used, resulting in a total number of 240 trials. Each semantic item had a corresponding evaluative item regarding the topic. Half of the items were positive assertions and the other half negative ones. Stimuli were presented in a randomized order every 6 s on average. In order to increase the temporal resolution, the trials were presented with variable onset-delays of 0, 400, 800, 1200 or 1600 ms. Stimulus sentences were displayed with a LCD projector on a back-projection screen mounted in the bore of the magnet behind the participant's head. Participants viewed the screen wearing mirror glasses. The sentences appeared on the screen for 2 s, after which they disappeared. Subjects were given a maximum of 4 s after stimulus onset to respond by pressing with the right index finger (Yes) or right middle finger (No). The screen remained blank between trials.

The experiment was performed using a 3T whole body scanner (Medspec 30/100, Bruker, Ettlingen). Functional images were acquired using a SE-EPI sequence (TR 2000 ms) with 16 axial slices (5 mm thickness, 1 mm spacing), parallel to the AC-PC plane and covering the whole brain. One functional run with 723 time points was measured, with each time point sampling over the 16 slices. Prior to the functional run, 16 corresponding anatomical slices were acquired.

The fMRI data were processed with LIPSIA software [13]. Functional data were corrected for motion and slice acquisition time differences. A temporal highpass filter with a cutoff frequency of 1/144 Hz and a spatial Gaussian filter with a full width at half maximum (FWHM) of 5.65 mm was applied. The anatomical slices were co-registered with the full-brain scan that resided in the stereotactic coordinate system and then transformed by linear scaling to a standard size. The transformation parameters obtained from the registration were subsequently applied to the functional slices so that the functional slices were also co-registered into the stereo-

tactic space. This linear normalization process was improved by an additional nonlinear normalization [19].

The statistical evaluation was based on a least-squares estimation using the general linear model for serially auto-correlated observations [7]. The model equation, including the observation data, the design matrix and the error term, was convolved with a Gaussian kernel of dispersion of 4 s FWHM. Thereafter, contrast maps (i.e. estimates of the raw-score differences of the beta coefficients between specified conditions), were generated for each subject. As the individual functional datasets were all aligned to the same stereotactic reference space, a group analysis was performed subsequently. A one-sample *t*-test of contrast maps across subjects was computed to indicate whether observed differences between conditions were significantly different from zero [10]. Subsequently, *t*-values were transformed into z-scores.

For the evaluative conditions, it was not possible to differentiate between correct and false responses. Thus, all responses were considered for the evaluative as well as for the semantic condition. The resulting mean reaction time was 1860 ms (SE = 79 ms) for the semantic condition and 1857 ms (SE = 76 ms) for the evaluative condition; reaction times did not differ between conditions (Student's *t*-test; $t = -0.27$; $P = 0.79$).

First, we contrasted the semantic memory retrieval condition against the evaluative judgment task in order to replicate the findings of the previously presented study [20]. The results are summarized in Table 1 and in Fig. 1. The main regions activated specifically by the evaluative condition were the dorsal aMPFC (BA 9/10m) and the inferior pre-cuneus/posterior cingulate cortex (PCC); both regions correspond to those found in the previous study [20]. In addition, the dorsal aMPFC activation now extends further ventrally into the ventral aMPFC (Fig. 1). This activation was located in the ventral part of the cingulate sulcus. An additional activation was found in the fronto-opercular cortex. Minor activations were found in the superior frontal sulcus and in the left middle and superior temporal gyri. By using the SE-EPI sequence it was possible to show that the aMPFC activation extended into the ventral aMPFC and into the fronto-orbital cortex.

By only considering these activation maps, one cannot exclude that blood flow is decreased in both tasks. If the signal is attenuated to a greater extent in the semantic condition than in the evaluative condition, this would also result in activations in the aMPFC, even though none of the tasks really activates the aMPFC. To investigate this, we analyzed the underlying signal time courses in different regions of the aMPFC. To accomplish this, the aMPFC was split into four arbitrary sections from dorsal to ventral (Fig. 2). For each subject, significant activations (z -value >2.3 and a volume of at least 90 mm^3) in the aMPFC were allocated to one of the four sections, according to their location. The underlying signal time-course was extracted and the percent signal change was calculated in relation to the mean signal intensity

Table 1

Talairach coordinates, maximum z-value of the local maxima (volume of the activated region) for evaluative judgment vs. semantic memory retrieval^a

Area	Talairach coordinates	Z-max (volume)
Anterior medial prefrontal cortex	5 49 16	5.42 (1938)
Ventral medial prefrontal cortex	-11 42 -2	4.34 (882)
L. fronto-orbital cortex	-13 62 1	4.19 (267)
L. superior frontal sulcus	-25 45 28	3.91 (181)
Precuneus/PCC	-3 -47 28	4.83 (1249)
L. fronto-opercular cortex	-40 14 -7	4.41 (538)
R. fronto-opercular cortex	32 21 -9	4.18 (209)
L. anterior superior temporal gyrus	-45 7 -17	3.74 (246)
L. anterior middle temporal gyrus	56 -8 -14	4.61 (664)
L. posterior superior temporal sulcus	40 -31 2	4.90 (385)

^a To protect against false positive activations, only activations with a z-value > 3.1 ($P = 0.001$, uncorrected) and with a volume greater than 180 mm^3 (four voxels) were considered.

across all timesteps. The percent signal change was averaged for each condition and region and averaged over all subjects. The time course of the non-events was subtracted from the averaged time-courses. Then, the mean percent signal change for the period of 3–8 s after stimulus onset was calculated. The results clearly indicate that signal intensity increased in all regions of the aMPFC in the evaluative task, and was attenuated in the semantic task (Fig. 2). The signal decrease in the semantic condition is not necessarily a ‘deactivation’ (i.e. reduction from baseline) of this area during the semantic task, as the mean signal intensity does not reflect a resting baseline. It might represent the falling slope of the hemodynamic response of the previous trial, which in half of the trials was an evaluative judgment task. The signal increase in the ventral aMPFC partly contradicts the notion that the aMPFC is suppressed during attention-demanding cognitive tasks [4,18]. Simpson et al. [18] argued that blood flow changes in the aMPFC can be interpreted as the interaction between attention-demanding cognitive activity and performance anxiety. By this, any attentional task could lead to accompanying activations in the ventral aMPFC. In the present study it seems unplausible to assume that the semantic condition is less attention-demanding and

causes less anxiety than the evaluative task. However, there is a major difference between the two conditions contrasted in the present experiment. The response in the semantic condition is evident and can be retrieved from memory. In contrast, the evaluative condition requires a new response to be generated on the basis of the subject’s internal value system and given facts. Some sort of feeling of ‘rightness’ [5] has to be generated rather than a merely rational analysis of given facts as in the semantic condition. It appears that the dorsal aMPFC is mainly involved when, due to insufficient information, the appropriate course of action has to be determined [5]. Further, the dorsal and ventral aMPFC are not necessarily differentially activated. The ventral aMPFC is not necessarily attenuated during attention-demanding processes, but rather co-activates along with the dorsal section if the internal value system is addressed. One could argue that the ventral aMPFC activation represents processes induced by thinking of a subjectively relevant situation or fact [12]. However, the same responses should be evoked during the semantic and evaluative condition, provided that the same situation or fact is retrieved. It appears that under certain circumstances, the ventral aMPFC is co-activated with the dorsal aMPFC, which is not due to performance

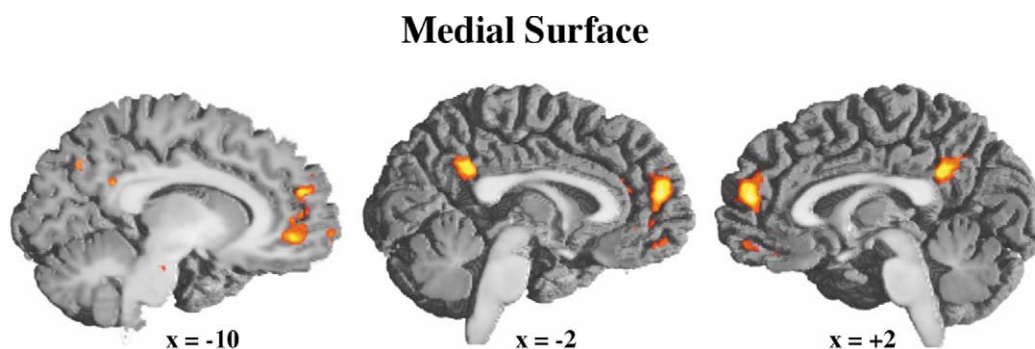


Fig. 1. Averaged activation maps of the main contrast evaluative judgment vs. semantic memory retrieval mapped on to the reference brain. Three sagittal slices of the medial surface with the main activations in aMPFC and precuneus are shown. The z-value were thresholded at $z = 3.1$ ($P = 0.001$, uncorrected).

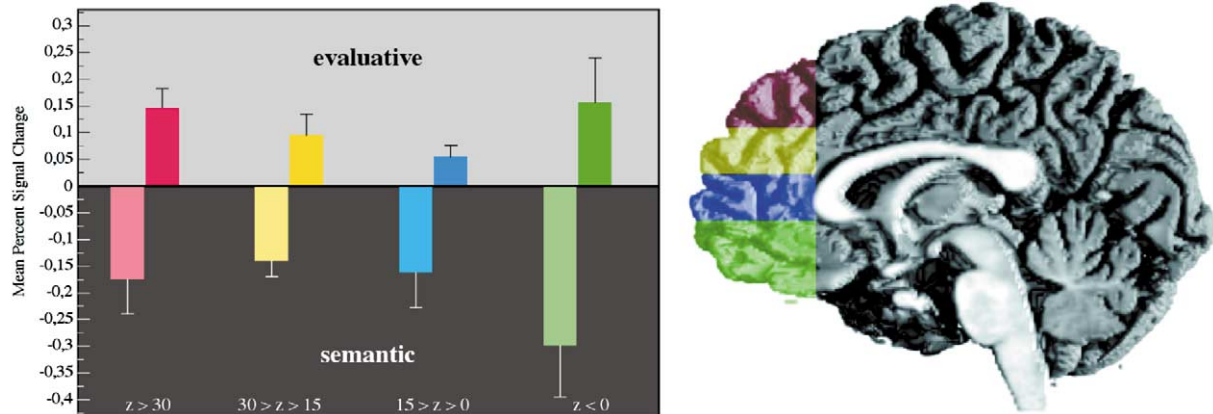


Fig. 2. The four arbitrary sections of the aMPFC are color shaded (right). Mean percent signal change (and standard error) for the semantic memory retrieval and evaluative judgment condition (left) for the four arbitrary sections are shown, colored according to the four sections. In all four sections, the mean signal intensity differs significantly between the evaluative and semantic condition (paired *t*-test; $P < 0.01$).

anxiety or emotional arousal, but rather to task-specific aspects.

In conclusion, the present findings showed that evaluative judgment not only activates the dorsal aMPFC, but that the activation extends into the ventral aMPFC. Thus, the ventral section seems to be involved both in attention-demanding processes and evaluative judgment. This does not exclude the possibility that a factor like the subjective significance of the content of a sentence is relevant, which in everyday life is often confounded with formal self-reference.

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