

Cognitive processes and cerebral cortical fundi: Findings from PET studies
(brain/neuroanatomy/positron emission/cortical sulci)

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ABSTRACT

Positron emission tomography (PET) studies of regional cerebral blood flow have provided evidence relevant to localization of cognitive functions. The critical loci identified in these studies are typically described in terms of macroanatomically labeled cortical and subcortical regions. We report the results of a meta-analysis of localization of changes in blood flow, based on nearly 1,000 cerebral cortical peaks of activity obtained from groups of subjects in 30 PET studies. The results showed that, on average, 47% of these peaks were localized within the fundus regions of cortical sulci. This is an unexpectedly high proportion, because fundal regions comprise less than 8% of the cortical mantle. Further analysis suggested a coarse correlation between the extent of fundal activation observed in different studies and the estimated cognitive complexity of the tasks used in the studies. These findings are potentially interesting because (a) the preponderance of fundal activation has implications for the interpretation of the PET data, (b) they suggest that cortical sulcal and fundal regions may play a distinctive role in higher cognitive processing, or (c) both of the above.

In a recent ¹⁵O-positron emission tomography (PET) activation study of episodic memory (1) we made an incidental observation that we thought was interesting. The pattern of cortical blood-flow differences between two tasks—listening to previously presented versus previously not presented sentence-like verbal constructions—showed that a surprisingly high proportion of the peaks of neuronal activity associated with remembering of the sentences seemed to be located in the depths of cortical sulci rather than on the gyral surface. Even more surprising was the observation that sulcal activation frequently seemed to be concentrated in the deepest parts of sulci, that is, in the fundus regions.

These observations were remarkable for one or more of three reasons. First, the observations imply a degree of precision of localization of function that is generally thought to be well beyond the spatial resolution of the PET technique. This is why activated regions are usually described in gross terms, such as 'right parietal lobule' or 'Brodmann's area 6.' Specific gyri and sulci, let alone specific regions in them, are seldom mentioned (for one exception see 2). Second, one 'obvious' possible explanation of these observations was that they reflected some basic but hitherto unknown or unsuspected artifact of the PET technique. Third, and most intriguing, was the possibility that the fundus regions of cortical sulci, known to have special histological and hodological properties, may play a special role in cognition. Therefore, although we were acutely aware of several a priori reasons why the undertaking might not be expected to succeed, we decided to pursue the matter of fundal activation further, on a somewhat more extensive scale. This article tells the story of what we did, what we found, and what we think it might mean.

METHODS

The local topography of the cerebral cortical mantle consists of four kinds of regions: (i) the crown (or culmen), (ii) the shoulder (or angulus or lip), (iii) the wall (sulcus, fissure) and (iv) the fundus region. The crown region lies on the outer surface (on the convexity) of the brain, the shoulder is the cortical bending that connects the crown and the wall, the wall is the cortical surface within a fissure or a sulcus, and the fundus region is the bottom (deepest point) of a sulcal indent. For reasons just mentioned, we focused on the PET activations in the fundi.

The findings we describe and discuss in this article were derived from a meta-analysis of the published PET studies. The initial question posed was simple: How frequently does fundal activation occur? To answer the question we examined published data for evidence of fundal activation. Including our own study (1) that prompted the exercise, we selected a sample of 30 PET activation studies that (i) were readily accessible to us, (ii) had used the ^{15}O -labeled water technique of PET, and (iii) reported the locations of observed peaks of activation in the co-ordinates of the Talairach et al. (2) or the Talairach and Tournoux (3) stereotaxic atlases of the human brain. The total number of peaks of cortical activation reported in the 30 studies was 981.

Our procedure was as follows. We pinpointed the position of each of the 981 peaks of activation in all three dimensions-- horizontal, coronal, and sagittal--in the stereotactic brain atlas of Talairach and Tournoux (3). When the coordinates in a particular report were given on the basis of the previous edition of this atlas (2), we used that atlas or converted the coordinates. On the basis of its pinpointed position, each peak was classified as representing either 'fundal' activation (within or near the fundus region) or 'nonfundal' activation (crown, shoulder, or sulcal wall of the cortex, or subcortical loci).

Successive cross-sections in the atlas of Talairach and Tournoux are spaced 1 mm to 5 mm apart, depending upon the plane (horizontal, sagittal, or coronal) and the distance from the midcommissural level (3). A set of coordinates was classified as representing fundal activation if (i) its location on one or more planes (horizontal, sagittal, or coronal) in the Talairach and Tournoux (3) atlas lay within 2 mm of the virtual center of a fundus, and (ii) if the sulcus in question had a depth of at least 6 mm. The 2-mm criterion was relaxed to 4 mm in cases in which interpolation between different planes was necessary. The 6-mm criterion of sulcal depth overlooks developmental considerations (4); we adopted it on purely pragmatic grounds, for the sake of simplifying a complex issue at the initial stage of its pursuit.

RESULTS

The findings of the exercise are summarized in Table 1. For each study in our sample, Table 1 specifies (i) the number of peaks of activation (sets of coordinate points in the cerebral cortex), (ii) the proportion of these points that were classified as showing fundal activation, and (iii) the general category of the cognitive tasks used. Unless otherwise indicated in Table 1, all studies were done with normal healthy subjects.

Insert Table 1 about here

The data of central interest are the proportions of peaks classified as showing fundal activation. We will refer to this proportion as the 'fundal fraction.' We note two central facts concerning fundal fractions. First, the overall weighted mean of the fundal fraction for the studies listed in Table 1 is 47%. The weighted mean takes into account the number of observations provided by different studies. (The unweighted mean, which weights the calculated fundal fractions from all studies equally, is somewhat lower at .41.) Second, the range of fundal fractions yielded by individual studies was large, extending from 0 in three studies to .60 and above in five studies. This range suggests that something else other than random fluctuations around a stable mean are responsible for the variability.

One possibility for this 'something else' is the nature of cognitive activity required by the tasks used in different studies. To explore this possibility we grouped the studies into three categories on the basis of the terminology and task descriptions provided by the authors of the studies, as shown in Table 1. The 11 studies in the first category (5-15) involve basic motor and sensory functions or comparisons between normal and psychologically or neurologically abnormal subjects. Thirty per cent (range 0%-59%) of the 166 reported activity peaks in this group fell in the fundus regions. The second group of 11 studies (16-26) involved tasks having to do with attention, complex motor or perceptual acts (e.g., imagery), and language processing. The 611 peaks in this group yielded a weighted mean of 47% (range 38%-65%) of fundus-related activity. In the third group of 8 studies (1, 27-33) dealing with memory and problem solving, 60% (range 42%-75%) of the 169 reported activity peaks were classified as fundus-related.

These data suggest a possible correlation between computational complexity of mental tasks and fundal fractions as revealed by PET studies. Although the evidence is somewhat fragile, based as it is on a haphazard collection of studies, variable numbers of observations reported by these studies, the possibly questionable classification of task situations used in the studies, and the largely intuitive assessment of computational complexity of the processes underlying the tasks, it is sufficiently intriguing to be worth further thought.

What do these findings mean—the relatively high mean fundal fraction, the wide range of fundal fractions across different studies, and a possible coarse correlation between fundal fraction and computational complexity of task situations? We consider three possible categories of interpretation: (i) the findings are not real, they represent nothing more than experimental 'noise,' (ii) the findings are real, but they arise for reasons that have little to do with the physiology or psychology of brain function, and (iii) the findings have physiological and psychological significance, and they point to a special role that fundus regions of the cerebral cortex play in neural computations underlying mental experience and cognition.

ARE THE FINDINGS REAL?

A number of experts in the field of positron emission tomography who are aware of our 'fundus story' have expressed serious doubts about its reality. The main problem, these critics claim, has to do with the precision of localization of blood flow that our procedure and findings imply. A long list of reasons can be given why this kind of precision is simply not possible.

The PET-technique itself has various degrees of spatial resolution, depending on the apparatus used and possibly also depending on the particular region of the brain under study (34, 35), but in general the resolution is just too poor to allow the kind of precision that our procedure requires and the results imply. Anatomical variations in the location of sulci between brains, and between the hemispheres of individual brains, possibly exaggerated by brain pathology, are well known (3, 12, 36, 37). Functional inter-subject variability has been reported even for motor skills (38). This variability cannot wholly be compensated by the three-dimensional proportional system used in the atlas of Talairach and Tournoux (3), and it may be even enhanced by the 'translation' between atlases. Averaging across subjects and across studies compounds the difficulties of localization (39). Peak coordinates only designate the locus of maximal activation and ignore the gradients of blood flow around the peaks. The algorithms used for averaging PET-data may differ between laboratories. Significance levels for given activation peaks differ (and may also differ between studies). The sizes of samples of subjects, which naturally vary between studies, affect the reliability of the data.

All these and other related facts and conjectures appear to rule out the possibility of precise localization of peaks of activation, and therefore militate against the very undertaking of an exercise of the sort that we describe here.

We assume that our basic findings are real. The proportional grid system used in the construction of the Talairach and Tournoux (3) stereotaxic atlas apparently achieves a normalized system applicable to the 'averaged brain' of a group of subjects. Moreover, considerable inter-subject consistency in cortical organization has been reported, and there is evidence that such consistency holds for regions at different distances from the neural center (40). Most important, however, is the fact that our exercise as described did produce systematic empirical data: order seldom arises from chaos. Indeed, we think that the reasons advanced against the impossibility of our exercise are likely to be responsible for an underestimation of fundal fractions in individual studies.

ARTIFACTS OF TOPOGRAPHY AND BLOOD SUPPLY?

It is conceivable that our findings reflect (i) the topographically expected values of fundal fractions, (ii) volumetric factors determining blood flow measurement in PET studies, or (iii) correlation between the volume of blood flow and changes in blood flow in different regions of the brain. We discuss these possibilities in turn.

A fundamental characteristic of the human cerebral cortex is its extensive gyrification. Only about 40% of the cortical mantle is exposed to the gyral surface, the remainder is 'hidden' within numerous fissures and sulci (1). Therefore it would be natural to expect that the majority of loci of cortical activation revealed by PET studies of cognitive processes would also lie within cortical sulci.

Does the observed average fundal fraction (47% for the present sample) simply reflect what would be expected if activity peaks were spread evenly across cortical topography? Facts suggest that the answer is 'no.' The fundus, as we have defined it here, represents a relatively small proportion of the sulcal surface, and, of course, an even smaller proportion of the cortical surface. We have calculated on the basis of the results of Zilles et al. (41) and on the basis of the atlas of Talairach and Tournoux (3) that fundus regions constitute less than 12% of the sulcal surface. Zilles et al. (41) found that the sulcal regions total something like 60% of the cortical mantle. Therefore, given a cortical activation, the expected probability of observing sulcal activation should be around 60%, and fundal activation 12% of the 60%, or less than 8%. Our observed value of 47% is almost six times as high, encouraging us to look for more substantive explanations of the findings.

Another factor responsible for the fundal findings may have to do with the partial-volume effect. This effect refers to the relation between object size and physical image resolution. When the object size is at least as big as the resolution volume of the individual elements measured by the PET scanner, the image will reflect both the absolute amount and concentration of activity. For smaller objects, only the amount, but not the concentration of activity will be truly reflected (35). Fundus areas usually have more tissue volume than non-fundal areas. Therefore it is possible that high levels of blood flow found in fundus regions indicate a partial volume effect.

The possibility of partial volume effects as responsible for the prevalence of blood flow changes in the fundus regions cannot be ruled out at the present time. Only further research can clarify the matter. Note, however, that if the partial volume hypothesis turns out to be correct, whether wholly or partially, it would have important implications for the practice and technique of neuroimaging, and for the interpretation of the blood flow data: It

would mean that, to an unknown extent, PET measurements reveal how the cortex is folded rather than where cognitive processing occurs.

We are not convinced that the partial volume effect is responsible for our findings, at least not wholly so. It does not fit the pattern of data showing a wide range of fundal fractions. If PET activations are localized to fundal regions because of partial volume effects, and not because of computational requirements of the tasks under scrutiny, the fundal fractions of different studies would be expected to be more uniform than they actually are.

A third plausible 'artifactual' reason for the findings is related to the course of blood vessels and their arterial branches running below the arachnoidea. Thus, peaks of activation may tell us more about the loci of initial blood transfer to the cortex, or the microcirculation in the capillaries, than about the synaptic activity that accompanies changes in neuronal activation.

A concrete example of the possibility that changes in blood-flow may indicate the presence of a major vessel is provided by the widely observed activity peaks along the cingulate sulcus (e.g. 1, 7, 9, 16-18, 22, 24, 25, 27-29). Actual brain photographs provided in the atlas of Ono et al. (36) reveal considerable interindividual variability in the course of major arteries in this area, thus leaving open the possibility that PET activations of the cingulate sulcus reflect the presence of arterial 'channels.' Again available evidence does not rule out a causal relation between the volume of blood flow and changes in blood flow in specific regions of the brain. However, if the arterial pathway hypothesis were true, then, like the partial-volume hypothesis, it would have serious implications for the usefulness of the PET technique for localizing cognitive functions. It would mean that PET data reflect largely the course of arterial pathways rather than, or perhaps in addition to, differences in synaptic activity (34, 42).

We have reservations about the arterial pathway hypothesis for the same reason that we were skeptical about the relevance of the partial-volume effect: It is at variance with the extensive range of fundal fractions in different studies.

In summary, then, at the present time we cannot exclude the possibility that the high average level of fundal activity reflects either the partial volume effect or the course of blood vessels in the brain, although we remain sceptical about it. If we are wrong, and our findings are 'artifactual', the implications for PET studies of cognition would be profound. Future research will undoubtedly clarify the picture. Pending such clarification we contemplate prospects that are theoretically more interesting.

FUNDAL COGNITION?

We now examine the conjecture, suggested by the observed coarse correlation between fundal fraction and apparent cognitive complexity of tasks used, that fundal peaks of activation mark the hubs of cortical computations (43) that subserve behavioral, cognitive, and experiential processes. A corollary of the conjecture is that the extent of fundal activation across studies, as reflected in the proposed index of fundal fraction, covaries with the computational complexity of behavioral and cognitive tasks. We refer to the conjecture and its corollary as the hypothesis of fundal cognition. Although direct evidence for the hypothesis clearly is quite frail, it receives indirect support from some other observations that have been made about the brain. We consider them under the following categories: (i) Possible implications of the variability of gyrification of different brain regions, (ii) possible relevance

of specific anatomical characteristics of the fundus regions, and (iii) the relation between cognitive processes and fundal activation.

Gyrification. Evolution has resulted in an intensely gyrified cortical mantle within the human brain. The degree of cortical folding can be expressed quantitatively. Zilles et al. (41) proposed a gyrification index (GI) for the cerebral cortex which is composed of the length of complete cortical contour, divided by the length of outer contour. The mean GI increases from prosimian to human brains and reaches the mean value of 2.56 in humans.

The high value of GI suggests that sulcus-related blood-flow changes should be much more probable than crown-related changes. However, as we argued earlier, even this high GI value is not sufficient to account for the proportion of sulcal, and in particular of fundus-situated activity peaks in PET data.

The anterior and posterior portions of the cerebral hemispheres are somewhat more extensively gyrified than the middle portions. We used this fact to examine the relation between degree of gyrification and frequency of fundus-related activity changes. We did so on the basis of the study of Corbetta et al. (18) who reported a conveniently large number of 135 activated 'spots' within cerebral cortical areas. We found no relation. Indeed, the observed trend was in the opposite direction: The primary visual area and surrounding regions in their Table 2 showed only 25% fundus-related loci.

Special Character of Sulcal and Fundal Regions. The thickness of the cerebral cortex is not uniform. Differences in the thickness and extent of different portions of the cortical mantle have attracted researchers since the turn of the century (44). Sanides (45) pointed out that discontinuous morphological changes are located, as a rule, in the depths of the indentations of the cortical surface. He emphasized that the boundaries of fields appear near the floor of the sulci, that is, in the fundi. The fundus is the least specific region of the cortex with respect to its architectonic appearance, and therefore areal borders are difficult to establish within the fundus region (45, 46, 47).

The physiological significance of this anatomical fact has been known for some time (48) and was confirmed in a large number of later studies, summarized by Welker (49).

The fundus as the boundary between distinct architectonic areas hints at its special role in intracortical communication (49-51). In fact, most of the cyto- and myeloarchitectonic cortical maps with highly diversified areal delineations have relied on sulci as demarcations (e.g., 52-54). Vogt and Vogt (55) provided 217 cytoarchitectonic fields for the human cortex. Beck (56) differentiated 77 myeloarchitectonic areas just within that portion of the chimpanzee's temporal lobe situated in the Sylvian fissure. And Brodmann (57) had indicated before his untimely death that he intended to divide areas further, in fact he already had done so by adding area 12, and dividing area 7, in publications following his standard monograph (see 58, 59).

The fundus regions show dramatic changes in comparison to the crown regions: Typically, the cortical thickness in the fundus region is reduced by 40-50% in comparison to the culmen region, and the volume of the neuropil decreases (4). Especially the two deep layers whose neurons project largely to brain stem and other subcortical regions, are greatly reduced in thickness, concomitant with a reduction in fiber richness (45, 51).

The fundus regions are lacking in dense thalamocortical connections (49), are primary recipients of interhemispheric cortical afferents (60), and have a higher perikaryal density than the gyral crown cortex (4). Sulcal and therefore fundal development apparently depends on the ingrowth of thalamocortical and corticocortical connections during fetal development (61, 62). In the crown regions of the cortex the somata are farther apart vertically and horizontally, and the cell columns are more pronounced, than they are in the fundi. Myelinated fibers in the crown regions are more conspicuous and have a denser terminal arborization than in the fundal cortex (4). On the other hand, the horizontal ramification of basal dendrites seems to be more extensive in fundus regions (4).

These and related observations (63-65) suggest that the fundus zones constitute ideal places for intracortical (and therefore 'higher-order') communication. The preservation of the more superficial layers, primarily the second and the third transmitting intracortical communication [especially 'feedforward connections'; (65)], together with the reduced subcortical output (via the shrunken layers V and VI), add further support to this hypothesis of fundus regions as hubs of crosscortical traffic.

Convergence Zones. Finally, a number of researchers have pointed out that sulcal areas of the association cortex may constitute special convergence zones, that is, zones that receive dense 'converging' connections from other high-order cortical regions (67-69). Our results hint at the possibility that the fundus-related activity peaks are located in high-order convergence zones rather than in primary or secondary sensory or motor areas. It is possible to speculate that the nodal points of feedforward and feedbackward connections of storage and retrieval circuits of the sort proposed by several authors (43, 70, 71) are situated within such fundus regions of the cerebral cortical sulci. A related possibility is that fundus regions constitute the nodes of a neuronal net involved in the representation of learned information.

CONCLUSION

We have described findings from 30 PET studies showing (i) a high average degree of activation of fundal regions of cerebral cortical sulci, (ii) a wide range of this activation, expressed in terms of 'fundal fraction,' across the different studies, and (iii) a coarse correlation between fundal fraction and the deemed complexity of cognitive processes.

Some of the possible explanations of the findings can be regarded as 'artifactual' or at least largely devoid of physiological or psychological significance. Two of these—partial volume effect and the course of blood vessels in sulci—are plausible and cannot be dismissed yet, although they seem to be inconsistent with the observed wide range of values of fundal activation across different studies. Other kinds of evidence suggest that fundus regions are hubs of cortical 'traffic' of information.

We suggested a functional hypothesis that we refer to as the hypothesis of fundal cognition: More demanding and complex cognitive functions—with respect to processes such as attending, encoding, retrieving, analyzing, evaluating, and interpreting information—rely on cortical fundal activity to a higher degree than do less demanding processes. More specifically we suggest that computational complexity of mental tasks is correlated with fundal activation as reflected in the measure of fundal fraction. The principal purpose of this article is to alert other interested cognitive neuroscientists to the existence of the data that suggested the hypothesis of fundal cognition, and to invite them to share in our own future efforts to learn more about 'fundal activation' and its possible explanations.

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Table 1. Number of cortical loci and percentage of activity change peaks related to fundi

Study	Main topic	Cortical loci	Fundal fraction*
<i>(1) Studies principally related to basic motor and sensory functions or to comparisons between normal and psychologically or neurologically abnormal subjects</i>			
Bench et al. (5)**	melancholia	9	22%
Colebatch et al. (6)	arm, hand movements	17	59%
Deiber et al. (7)	hand movements	21	43%
Frith et al. (8)	"willed action"	10	20%
Kew et al. (9)**	joystick movement	12	25%
Sergent et al. (10)	face/object processing	37	22%
Talbot et al. (11)	pain	4	0%
Watson et al. (12)	visual discrimination	4	0%
Weiller et al. (13)**	hand movements	23	39%
Zatorre et al. (14)	olfactory perception	6	0%
Zatorre et al. (15)	auditory discrimination	23	26%
<i>Weighted Mean</i>		<i>166</i>	<i>30%</i>

(2) Studies principally related to attention, complex motor or perceptual acts (), and language processing

Bench et al. (16)	attention	16	38%
Corbetta et al. (17)	attention	136	44%
Corbetta et al. (18)	spatial attention	135	53%
Démenot et al. (19)	language	30	53%
Kosslyn et al. (20)	imagery	52	46%
Kosslyn et al. (21)	object identification	42	43%
Pardo et al. (22)	attention	37	41%
Pardo et al. (23)	attention	12	50%
Paus et al. (24)	"higher-order motor control"	114	42%
Petersen et al. (25)	language	31	65%
Zeki et al. (26)	visual processing	6	50%
<i>Weighted Mean</i>		<i>611</i>	<i>47%</i>

(3) Studies related to problem solving and memory processing

Buckner et al. (27)	verbal memory	35	60%
Grasby et al. (28)	verbal memory	19	47%
Nichelli et al. (29)	chess play	38	63%
Paulesu et al. (30)	working memory	10	40%
Petrides et al. (31)	memorizing abstract designs	12	42%
Petrides et al. (32)	working memory	14	57%
Smith & Jonides (33)	working memory	8	75%
Tulving et al. (1)	recognition memory	68	68%
<i>Weighted Mean</i>		226	57%

Notes: * Fundal fractions are weighted means of proportions of fundus-related activities, calculated by taking into account the different numbers of cortical loci in different studies.

** Studies based on psychiatric or neurologic patients.

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