Orbital Versus Dorsolateral Prefrontal Cortex

Anatomical Insights into Content Versus Process Differentiation Models of the Prefrontal Cortex

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ABSTRACT: Content differentiation models posit that different areas of the prefrontal cortex perform similar operations but differ in terms of the content that is operated on. For example, it has been suggested that the orbitofrontal cortex (OFC) and the dorsolateral prefrontal cortex (DLPFC) perform similar working memory or inhibitory operations, but on different types of content (e.g., reward versus spatial or feature-based versus abstract). In contrast to the above models, process differentiation models posit that different areas of the prefrontal cortex perform fundamentally different operations. Surprisingly, discussions of these dueling models rarely incorporate information about anatomy. The only exception is that advocates of content differentiation models appropriately note that different parts of the prefrontal cortex receive different afferents. Yet, an examination of the anatomy of the OFC and the DLPFC reveal numerous differences in cortical structure and interneuron composition. These structural differences necessitate that the OFC and the DLPFC will have strikingly different computational features. Given such computational differences, strong versions of content differentiation models are untenable. While overarching themes may help explain the operations in both the OFC and the DLPFC, the specific operations performed in the two regions are likely to be both quantitatively and qualitatively different in nature.

KEYWORDS: cytoarchitecture; decision making; interneuron; orbitofrontal; working memory

As its name implies, the orbitofrontal cortex (OFC) is part of the frontal lobe. While that simple anatomical conclusion is unavoidable, theoretical models

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Ann. N.Y. Acad. Sci. 1121: 395–406 (2007). © 2007 New York Academy of Sciences.
doi: 10.1196/annals.1401.012

of frontal-lobe functions have often stumbled in their attempts to integrate the OFC with other aspects of prefrontal processing. Even in the latter half of the 20th century, it was not unusual for researchers to describe the OFC as an enigma. Indeed, the most significant predecessor to the present conference was a 1998 symposium entitled The Mysterious Orbitofrontal Cortex. This mysteriousness was particularly apparent when comparing what was known about the OFC relative to other prefrontal regions. When more dorsolateral prefrontal cortex (DLPFC) regions came to be associated with classic frontal measures, such as the Wisconsin Card Sorting Task,[1] lesions of the OFC rudely failed to produce typical perseverative errors.[2] Similarly, as studies in monkeys implicated the area around the principal sulcus in delayed spatial response tasks, animals with OFC lesions failed to show such deficits.[3]

OFC lesions not only failed to produce deficits on standard frontal measures, but also produced deficits on other measures that were not affected by DLPFC lesions.[4–7] This posed a major problem for early models of prefrontal functions, which emphasized the idea that the prefrontal cortex has a relatively unitary function. The observation of double dissociations between OFC and DLPFC lesions made such unitary models relatively untenable, and by the 1970s such models had given way to models that posit functional heterogeneity.[8,9]

Nevertheless, the idea that there is a unitary theme relating different frontal areas has remained popular. For instance, in her classic monograph on the prefrontal cortex, Goldman-Rakic[10] proposed a *content differentiation* model of prefrontal regions. Content differentiation models hold that all prefrontal areas perform similar processes (i.e., operations or computations) but differ in terms of the input (type of representation) on which they act. In line with this conceptualization, Goldman-Rakic[10] put forth that different areas of the prefrontal cortex perform similar working memory operations but operate on different types of representations. Whereas the DLPFC operated on spatial information, a more ventrolateral region operated on object information, and orbital areas operated on emotional information. In support of such a conceptualization, delay period activity has been found during single cell recordings of nonhuman primate OFC.[11–13] This activity appears critically linked to the current reinforcement value of the expected reward, as opposed to simply representing the identity of the reinforcer.[12] Importantly, this delay period activity qualitatively differs from that typically seen in the DLPFC. Whereas DLPFC activity is characterized by sustained tonic elevations during delay periods, only a minority of OFC cells shows this type of sustained activity.[13] In contrast, the majority of delay period activity in the OFC follows an ascending or descending firing pattern in advance of the expected reward delivery time. Taken together, these findings suggest that a substantial portion of the OFC's delay activity reflects a reward expectancy. These expectancies may be updated and brought forth on a trial-by-trial basis, but they are not an exact parallel to the persistent activity associated with working memory in more dorsal regions. It is also notable that conceptualizations of working memory, especially in humans, include a manipulation component.[14] This allows us to manipulate the order of different pieces of information, such as numbers, letters, or spatial locations. While it is possible that we might select an order of rewards (for instance, choosing the order in which we wish to eat items), the parallel to the online reordering of information in other modalities seems limited. Just ask yourself: when is the last time you had a need to do an online manipulation of the order of expected rewards?

The beauty of Goldman-Rakic's[10] content differentiation model is that it provided an organizing principle for understanding the operations of different prefrontal regions. However, this model has been vigorously opposed by researchers who have instead argued for a *process differentiation* model for understanding frontal involvement in working memory.[15] Process differentiation models hold that different areas of the frontal lobe perform fundamentally different operations or computations. For instance, it has been proposed that specific prefrontal regions can be dissociated based on whether they are involved in the process of holding information online or in the operations necessary for the manipulation of internal representations.[15] The human neuroimaging data has proven difficult to reconcile with Goldman-Rakic's[10] original content differentiation model, as the process being performed has often appeared more important than the specific stimulus modality.[16,17]

An alternative content differentiation model of prefrontal involvement in working memory focuses on level of abstraction. Ranganath states, "all prefrontal cortex subregions play a role in selecting (i.e., accentuating or inhibiting the activation of) memory representations. . . . but that different subregions may be selecting information at different levels of analysis" (p. 280).[18] In contrast to Goldman-Rakic's[10] original model, Ranganath[18] proposes that rostral and dorsal prefrontal regions select representations of abstract relations between currently active items, whereas caudal and ventral regions select representations of relevant items. Overall, this model helps to explain the distributions of functional neuroimaging activations in many lateral areas, including ventrolateral regions along the inferior frontal gyrus. However, specific reference to areas along the orbital surface are absent from this model, and the neuroimaging data cited in support of the model focuses exclusively on lateral prefrontal regions. Thus, although all prefrontal regions are argued to play a role in a common process, the specific role of the OFC in working memory is left unspecified.

Content differentiation models have also been applied to decision-making tasks. In a pioneering study, Dias *et al.*[19,20] used an intradimensional/extradimensional shift task to isolate responses to changes within a dimension (stimulus reward reversal) and across dimensions (abstract rule changes). Marmosets with OFC lesions showed impairments only on the intradimensional shifts, while marmosets with DLPFC lesions showed impairments only on extradimensional shifts. The question naturally arises whether this reflects two different operations or similar operations being performed on different types of representations. Dias *et al.*[19,20] proposed a content differentiation model in which both the dorsal and the orbital areas are involved in inhibition, with the orbital area involved in inhibition of affective information (relating to previous rewarded stimuli) and the dorsal region involved in inhibition of attention (to the previously relevant dimension). Their 1997 paper states this model in the abstract: "These findings suggest that inhibitory control is a general process that operates across functionally distinct regions within the prefrontal cortex. Although damage to lateral prefrontal cortex causes a loss of inhibitory control in attentional selection, damage to orbitofrontal cortex causes a loss of inhibitory control in affective processing" (p. 9285).[20] Based on some other passages in the Dias *et al.*[19,20] papers, O'Reilly and colleagues[21] assert that Dias *et al.*'s[19,20] arguments actually conform to a process differentiation model in which the OFC is involved in affective inhibition, while the DLPFC is involved in attention selection. This distinction is not just semantic: in the original framework presented by Dias,[19,20] the DLPFC and the OFC are both argued to work through similar inhibitory operations, whereas O'Reilly's[21] presentation of the Dias model suggests that the attention selection mechanisms of the DLPFC work through other types of operations. Regardless of the accuracy of their characterization, O'Reilly *et al.*[21] themselves propose an alternative content differentiation model, which focuses on an abstract versus stimulus-specific gradient similar to that described above for working memory. Specifically, they propose that the DLPFC processes more abstract information, whereas the OFC processes more specific stimulus feature information. They argue that both areas use a dynamic gating mechanism to implement changes when contingencies change; the OFC implements changes when stimulus-reinforcer contingencies change, and the DLPFC implements changes when abstract (extra-) dimensional shifts occur. The feasibility of this model is supported by computational modeling that reproduces the double dissociation observed by Dias *et al.*[19,20]

In summary, while unitary hypotheses of prefrontal function have proven untenable, the extent to which the different prefrontal regions are engaged in similar or different types of operations remains a matter of debate. Both content differentiation and process differentiation models attempt to explain how different regions may be necessary for specific tasks, but these models stand in opposition in their characterization of the operations subserved by the different regions of the prefrontal cortex.

Anatomical Insights

In assessing the process differentiation versus content differentiation debate, it is helpful to consider the anatomical characteristics of the OFC and the DLPFC. At the most basic level, it is quickly apparent that different parts of the prefrontal cortex receive afferents from different regions.[22] Because of this, there are certainly some differences in the content of what is processed in different prefrontal regions. However, anatomical differences do not stop here. There are several fundamental anatomical factors that show that the computational characteristics of the OFC will be quite different from more lateral prefrontal regions. Whereas the DLPFC is composed of well-defined, six-layered, granular cortex (eulaminate II),[23] the OFC does not reach this level of definition. The most posterior aspects of the OFC are agranular, followed by dysgranular cortex (area 13, caudal area 14), and modestly to moderately defined granular (eulaminate I) areas in the more rostral and lateral aspects of the OFC (areas 11 and 12, rostral area 14).[23–25] In addition to differences in the extent of granularity, prefrontal areas differ in terms of neuronal density, relative amounts of neurons in superficial or deep layers of cortex, the ratio of neurons to glia, the ratio of feedback to feedforward afferents and efferents, and levels of parvalbumin and calbindin.[23,26] These neuroanatomical differences have substantial functional implications, including the degree of tonic activity, the extent of local circuit processing, the balance of excitatory to inhibitory processing, and the nature of input and output from the region.[23,26–28]

A full characterization of the anatomical differences between the OFC and the DLPFC is beyond the scope of this review, but several specific features warrant mention. The superficial layers of the DLPFC possess high neuronal density (FIG. 1). Importantly, the pyramidal cells in the superficial layers of the DLPFC possess widespread horizontal intrinsic axon projections, which have been proposed to form a critical substrate for recurrent lateral projections that produce persistent activity following a response to a preferred cue.[29–33] Such persistent activity forms the basis of working memory. In contrast to the DLPFC, the superficial layers of the agranular and dysgranular OFC possess far fewer pyramidal neurons.[23] Lacking dense lateral connections between pyramidal neurons, the dysgranular and agranular regions of the OFC probably do not possess the ability to maintain the sort of tuned persistent firing that is seen in the DLFPC.

Increasing data indicates that the types of interneurons in a region markedly influence the region's computational features.[32,34,35] Parvalbumin and calbindin are found in separate types of interneurons.[36,37] Critically, the densities of these different types of interneurons differs dramatically across prefrontal regions.[23] Parvalbumin levels double as one moves from agranular and dysgranular OFC to the DLPFC. In contrast, calbindin levels are approximately threefold greater in dysgranular OFC than in the DLPFC. Based on observed differences in the characteristics of interneurons, Wang *et al.*[32] argue that these parvalbumin and calbindin interneurons serve different functions in the prefrontal cortex. They note that within the DLPFC, parvalbumin-containing interneurons, presumably of the large basket-cell type, have fast firing characteristics and target the perisomal region of pyramidal cells. Based on computational modeling, Wang *et al.*[32] propose that the

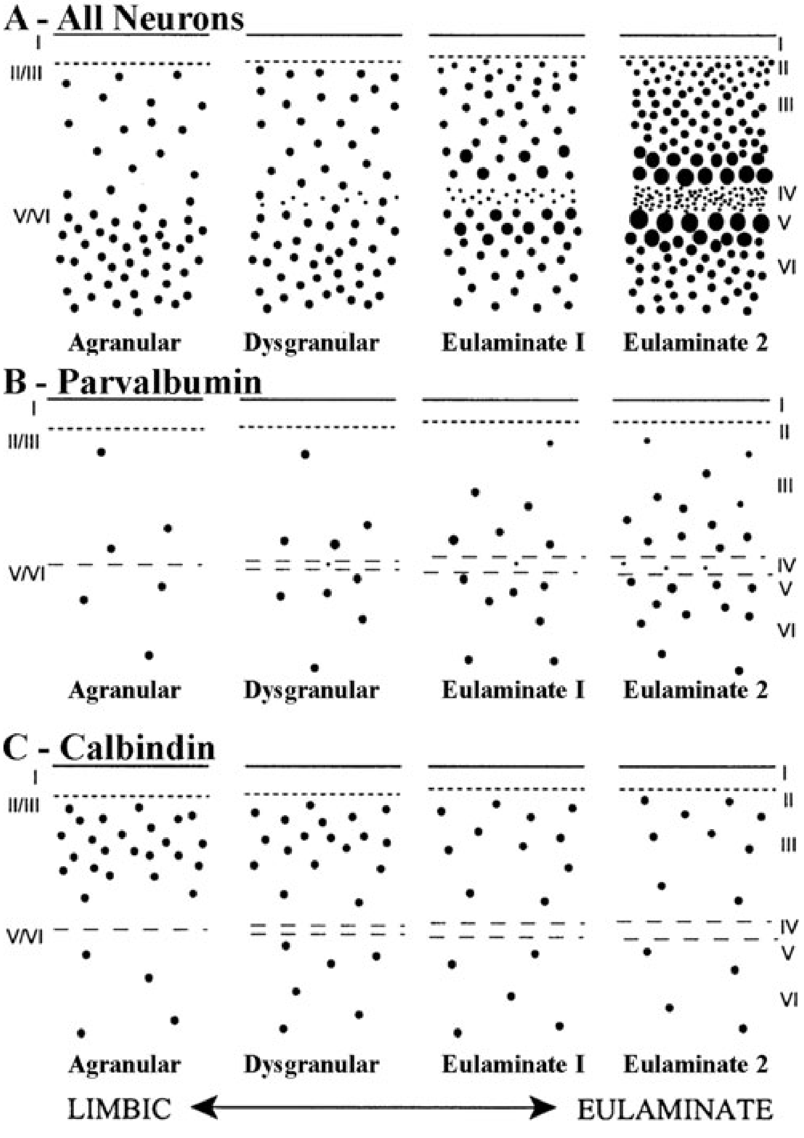

FIGURE 1. Differences in cell density (**A**), parvalbumin binding (**B**), and calbindin binding (**C**) in agranular, dysgranular, and granular prefrontal regions. The posteriormost aspects of the OFC are agranular, followed by dysgranular areas (such as area 13), and modestly to moderately defined eulaminate I cortex in the rostral and lateral OFC. The DLPFC is composed of eulaminate II cortex. The OFC has not only fewer cells but also very different ratio of calbindin to parvalbumin interneurons. (Figure adapted from Dombrowski, S.M., C.C. Hilgetag & H. Barbas. 2001. Quantitative architecture distinguishes prefrontal cortical systems in the rhesus monkey. Cereb. Cortex 11: 975–988,[23] with permission from Oxford University Press.)

parvalbumin-containing interneurons provide widespread perisomatic inhibition, which allows for stimulus (spatial) tuning of persistent activity during working memory. In contrast, calbindin-containing interneurons fire at a slower rate and target dendrites. Within their model, the calbindin-containing interneurons play a particular role in inhibiting interference from extraneous stimuli. Similarly elegant models are lacking for the OFC, but if we extend Wang *et al.*'s[32] reasoning, we would predict that the high levels of calbindin-containing interneurons in the OFC would lead to a network in which the inhibiting of extraneous information is robust. In contrast, the low levels of parvalbumin in the OFC would deprive it of the widespread inhibition necessary for tuning persistent activity.

Finally, the DLPFC and the OFC possess different levels of feedback and feedforward connections.[26,38] Feedforward projections can be defined structurally, in that they start from superficial layers and project to deep layers of cortex (FIG. 2).[39] In sensory systems, early stages of the processing stream provide information to subsequent stages through this type of feedforward projection. By contrast, feedback projections start in deep layers of cortex and project to superficial layers of cortex. Feedback projections act to modify or to bias the computations being performed in the earlier processing stages. For instance, feedback projections act to help accentuate the responses of cells coding attended objects or locations, while attenuating or suppressing responses to unattended objects.[40,41] Such feedback aids in basic perceptual processes such as figure-ground discrimination,[42] as well as allowing top-down control of what is processed in the information stream.

Based on analyses of the laminar patterns of axon projections, the agranular and dysgranular areas of the OFC are characterized by strong feedback

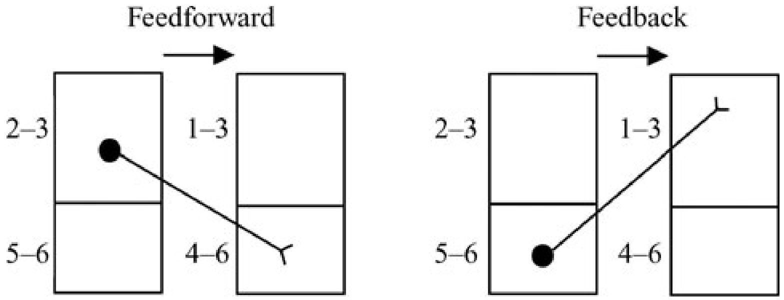

FIGURE 2. Feedforward versus feedback connections based on the laminar distribution of projections. Feedforward projections arise from superficial layers of cortex and project to deep layers of cortex. The projections carry information forward to later stages of the processing pathway. In contrast, feedback projections arise from deep layers and project to superficial layers of cortex. These projections allow modulation or biasing of early processing stages. The OFC efferents are more frequently of the feedback variety, whereas the DLPFC has a high percentage of feedforward projections.

features in their connections with other regions.[26,38] By analogy to sensory systems, this would mean that the OFC projections are geared toward biasing or modifying computations in earlier stages of information flow. By contrast, the eulaminate DLPFC has substantially higher levels of feedforward projections, which allow it to feed the results or output of its computations to subsequent brain regions. Thus, it appears the OFC and the DLPFC act upon other regions quite differently.

Taken together, the large number of anatomical differences between the orbital and dorsal prefrontal regions make evident that the orbital cortex has very different computational features than the DLPFC. Rather than simply performing similar operations on different types of input, these anatomical constraints indicate that the OFC's computational characteristics are both quantitatively and qualitatively different from the dorsal prefrontal regions. Thus, even if they are performing a similar type of operation on different content, the ways in which those operations are implemented are likely to be quite different. Such a conclusion is incompatible with a strong form of the content differentiation model, in which the computations or operations are considered to be equivalent.

CAVEATS AND CONCLUSIONS

I have argued that the anatomical differences between the OFC and more dorsal prefrontal areas make it unlikely that these two regions could perform equivalent computations. This conclusion runs counter to a strong content differentiation model that holds that the OFC and other prefrontal areas perform the same operations, but on separate input. In contrast, the anatomical differences would be fully compatible with a process differentiation model in which the two regions are held to perform fundamentally different operations. Such fundamental differences would be expected to lead to significant double dissociations in the effects of OFC lesions, which would extend beyond simple differences in content.

Before declaring a process differentiation model victorious, it is worth noting that a weaker content differentiation model is still viable. In a weak version of the content differentiation model, the OFC may be argued to perform operations similar to dorsal prefrontal regions, but with different computational properties. For instance, both the DLPFC and the OFC regions could perform operations necessary for inhibitory control, but using operations that differ due to the varied computational properties of the different regions. Indeed, it seems likely that different contents (such as abstract rules versus stimulus features) necessitate some computational differences in order to accomplish similar results. Ideally, such weaker versions of content differentiation models should specify the nature of these computational differences. Similarly, process differentiation models could afford to articulate the computational features that would be necessary to carry out different operations. At present, this remains difficult, as our knowledge of the precise computational features of various prefrontal regions remains quite coarse, but we can anticipate that our ability to specify these differences will increase dramatically in the coming years.

While I have focused on the anatomical arguments against strong content differentiation models, a similar line of reasoning could be used to target a strong process differentiation model that totally disregards differences in content. While some aspects of prefrontal processing appear quite multimodal in nature (allowing an area's operations to be performed on multiple types of stimulus representations),[43] differential inputs place constraints on the range of representations that can be processed in any given area. These constraints make a pure process differentiation model, in which all prefrontal regions are considered to operate on identical content, untenable. However, because knowledge regarding differential connections preceded the recent era of process differentiation models, it has generally been assumed (if not always stated explicitly) that inputs are not identical. In other words, while process differentiation models focus primarily on differences in operations, they are typically not predicated on the idea that the content itself is identical.

Perhaps a similar argument can be made that most proponents of content differentiation models also believe there are some differences in the operations being performed across regions. As such, it could be argued that the type of strong content differentiation model articulated in this article is really a "straw man" argument. Do theorists really believe that different areas of the prefrontal cortex are performing identical operations? O'Reilly *et al.*[21] state that different regions in their model perform a "common processing" function (p. 246). The word *common* leaves open the possibility of some computational differences among regions. Indeed, their model itself provides computational differences in the OFC and the lateral prefrontal areas (the OFC has more units in order to represent detailed features, and the lateral prefrontal has only enough units to represent the relevant dimensions). So it seems safe to assume that the authors did not intend to imply that the processes were identical in their computational properties. Thus, the model can absorb some degree of computational differences, as long as it can be shown that the basic architecture necessary to accomplish the common operations is present in both regions. The degree to which other content differentiation models accept computational differences is less clear. The sorts of qualifications that would indicate that the theorists intended a weak version of the model are rarely explicitly stated. If the theorists intended a weaker version of the content differentiation model, they do not state it. It seems safe to assume that many readers do not consider these unstated qualifications, and thus interpret the models in their strong form.

The argument put forth in this paper stands or falls on the degree to which the OFC and the DLPFC differ in their anatomical features. A quick glance at FIGURE 1 makes evident the strong contrast between the agranular/dysgranular OFC and the well-defined eulaminate II cortex that defines the DLPFC.

However, the degree of difference is weaker when one compares the eulaminate I cortex in the rostral and lateral OFC to the DLPFC. Does this mean that the arguments in this paper only apply to agranular/dysgranular OFC? No, but the argument is certainly strongest when contrasting more posterior and medial OFC regions to the DLPFC. Because transitions between different types of cortex occur gradually, computational features are also likely to vary gradually. Indeed, while maps of cortical areas often include sharp boundaries, in truth these boundaries are often gradual. The same is likely true for computational features. Neighboring regions may have computational features that differ in only mild quantitative rather than qualitative ways. However, as one moves through successive stages, the computational features and the operations they are capable of serving are likely to become progressively more differentiated. The difficulty in such a situation is determining at what point the anatomy or the operations that they serve has changed enough to consider them distinct.

This issue of boundaries is particularly tricky in regards to the ventrolateral prefrontal cortex. One could argue that while the content differentiation models have often been extended to the OFC, in the working memory literature, the greatest focus of debate has been on comparing the DLPFC with the ventrolateral prefrontal cortex rather than the OFC. Given the greater degree of similarity between the dorsolateral and ventrolateral prefrontal cortex, such areas are more likely to be able to perform similar operations. Even here, I maintain that care needs to be taken to look at the anatomical and resultant computational differences between these more proximal regions. Nevertheless, a content differentiation model is certainly more viable when comparing two areas of granular isocortex than when trying to extend such models to agranular and dysgranular regions of the OFC.

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