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Brain images used in this article (vmPFC mask) are available at <https://identifiers.org/neurovault.collection:5631>

A Brief Anatomical Sketch of Human Ventromedial Prefrontal Cortex

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The ventromedial prefrontal cortex (vmPFC) is a major focus of investigation in human neuroscience, particularly in studies of emotion, social cognition, and decision making. Although the term vmPFC is widely used, the zone is not precisely defined, and for varied reasons has proven a complicated region to study. A difficulty identifying precise boundaries for the vmPFC comes partly from varied use of the term, sometimes including and sometimes excluding ventral parts of anterior cingulate cortex and medial parts of orbitofrontal cortex. These discrepancies can arise both from the need to refer to distinct sub-regions within a larger area of prefrontal cortex, and from the spatially imprecise nature of research methods such as human neuroimaging and natural lesions. The inexactness of the term is not necessarily an impediment, although the heterogeneity of the region can impact functional interpretation. Here we briefly address research that has helped delineate sub-regions of the human vmPFC, we then discuss patterns of white matter connectivity with other regions of the brain and how they begin to inform functional roles within vmPFC.

vmPFC boundaries

An inclusive definition of the human vmPFC zone refers to the whole area of prefrontal cortex that is both ventral (i.e., $z < 0$ in standardized coordinate space) and medial (i.e., superior and inferior medial gyri, anterior cingulate gyrus, gyrus rectus, medial orbital gyrus, and the adjacent sulci; *Figure 1*). Quantifiable differences in the density of cortical layers IV and Va in postmortem human brains show distinguishable sub-regions within vmPFC^{1,2}. This research has yielded a useful map that builds upon the numbering scheme from the widely used Brodmann map, and provides a more fine grained specification of distinct areas within the vmPFC zone¹.

As in the Brodmann map, areas 24, 25, 32, 11, and 10 compose the vmPFC zone. In an effort to facilitate comparisons across species, newer specification further outlines medial, rostral, and caudal zones of area 14 (14m, 14r, 14c) within an area demarcated as areas 10 and 11 of the Brodmann map¹. As important as the delineation of areas within the vmPFC zone, there are spatial patterns in the histology within the vmPFC zone. Specifically, there are observable gradients such that anterior compared to posterior areas

Figure 1: Ventromedial prefrontal cortex structure and functions. A) A vmPFC mask (yellow) based on the Harvard-Oxford atlas¹⁹ and encompassing frontal pole, frontal medial cortex, subcallosal cortex, paracingulate gyrus, anterior cingulate gyrus and frontal orbital cortex. Areas dorsal to $Z = 0$ mm and lateral to $X = \pm 12$ mm are excluded. Parts of this vmPFC region are commonly activated across neuroimaging studies, with 3859 studies in the Neurosynth database reporting activation within our mask (April 6, 2016). B) To illustrate that vmPFC is involved with social, emotion, and economic valuation or decision making functions, we used the Neurosynth meta-analytic engine²⁰ and topic-based mapping²¹. We found vmPFC activation is significantly associated with each of these topics, suggesting that vmPFC activation is predictive of social, emotion, and decision-making functions. The vmPFC mask is available at <https://identifiers.org/neurovault.collection:5631>

of vmPFC show higher density of layer IV granule cells and medial areas show greater layer Va pyramidal cell density compared to areas more lateral on the orbital surface¹.

vmPFC connectivity

Observations of structural connectivity of the vmPFC zone demonstrate that (a) the vmPFC zone as a whole shows a pattern of connectivity that is distinct from other areas of prefrontal cortex, and (b) patterns of connectivity differ between sub-regions within the vmPFC zone. Detailed knowledge of structural connectivity relies largely on tracing methods in homologous areas of nonhuman primate brains, but comparisons to humans using noninvasive imaging methods support general similarities in prefrontal connections^{3,4}. Notably, there are few direct inputs from sensory regions to vmPFC, unlike lateral parts of orbitofrontal cortex^{2,5}, and weak connections with motor cortex, unlike lateral prefrontal regions³. There are prominent outputs from vmPFC to the hypothalamus, periaqueductal gray, amygdala, hippocampus, nucleus accumbens, and superior temporal cortex^{3,6}. Diffusion tensor imaging in humans has also identified long range connections between vmPFC and posterior cingulate cortex⁷. Structural connectivity patterns that differ between sub-regions of vmPFC include more prominent projections from amygdala to posterior areas of vmPFC (areas 24 and 25) compared to more anterior areas⁶. Ventral areas of vmPFC appear to connect more prominently with ventral and medial areas of striatum (i.e., nucleus accumbens) whereas more dorsal areas of vmPFC connect with anterior and dorsal areas of striatum^{8,9}. Additionally, vmPFC projections to hypothalamus are most prominent from posterior areas of vmPFC (i.e., area 25)⁶. A general observation of differences in connectivity patterns appears evident between anterior and posterior areas of vmPFC, which is consistent with the anterior-posterior differences in histology¹.

Understanding vmPFC from structure and connectivity

Functional distinctions – particularly with regard to emotional, social, and valuation processes – may map onto the structural distinctions that have been characterized in vmPFC. For example, anterior versus posterior areas of vmPFC have been suggested to represent different aspects of value, namely the experience of rewards and the decision between rewards, respectively^{10,11}. Meta-analytic tools are proving useful for looking into a large body of published research to identify how distinguishable areas of vmPFC may be associated with distinct topics, such as reward-related, social, affective or emotional and “default mode” functions¹² (see Figure 1). As evidence of such functional parcellations of vmPFC arrives, researchers can begin to explore how the functional distinctions map onto anatomical distinctions in vmPFC, taking into account its connectivity with other regions.

Functional relationships between vmPFC and other regions can clarify the psychological functions supported by areas within vmPFC. For example, posterior vmPFC connections with hypothalamus and amygdala form a network hypothesized to be important for regulating the stress response⁶. Neuroimaging research suggests a critical role for vmPFC (particularly more posterior subgenual areas) in regulating aversive responses, and in depression and posttraumatic stress disorder^{13–15}. Further research may elucidate how signals in the posterior area of vmPFC influence activity in hypothalamus and amygdala to determine physiological, emotional, and behavioral responses to stress, as well as how this system may be affected in disorders.

Knowledge of the regions co-activating and forming networks with vmPFC can help better describe the

Figure 2: Social, emotion, and decision-making functions involve regions beyond the vmPFC. We used Neurosynth²⁰ to contrast topics tied to social, emotion, and decision-making functions. Although these functions appear similarly associated with vmPFC activation, we found that regions beyond the vmPFC distinguished different functions. Specifically, activation within the posterior cingulate cortex (PCC) and temporal-parietal junction (TPJ) was more predictive of social topics compared to emotion or decision making topics. Likewise, compared to other topics, activation of the amygdala and striatum was more predictive of emotion and decision-making topics, respectively.

roles that vmPFC plays in the many functions linked with the region (see *Figure 2*). Indeed, recent meta-analytic work illustrates how distinct vmPFC functions modulate its co-activation with other regions: emotion increases vmPFC co-activation with the amygdala whereas social cognition increases vmPFC co-activation with the temporal parietal junction^{16,17}. These observations highlight how structural and functional imaging methods can combine to help characterize vmPFC function¹⁸.

Summary and outlook

The current state of knowledge of vmPFC structure and connectivity, including functional circuits described in nonhuman animals, sets the foundation towards understanding how vmPFC is involved in phenomena such as emotional, social, and decision making behaviors. Exciting future research is moving toward a more precise characterization of this heterogeneous and intrinsically important region in terms of structural, connectivity, and functional characteristics.

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