

## Anatomy and white matter connections of the orbitofrontal gyrus

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**OBJECTIVE** The orbitofrontal cortex (OFC) is understood to have a role in outcome evaluation and risk assessment and is commonly involved with infiltrative tumors. A detailed understanding of the exact location and nature of associated white matter tracts could significantly improve postoperative morbidity related to declining capacity. Through diffusion tensor imaging–based fiber tracking validated by gross anatomical dissection as ground truth, the authors have characterized these connections based on relationships to other well-known structures.

**METHODS** Diffusion imaging from the Human Connectome Project for 10 healthy adult controls was used for tractography analysis. The OFC was evaluated as a whole based on connectivity with other regions. All OFC tracts were mapped in both hemispheres, and a lateralization index was calculated with resultant tract volumes. Ten postmortem dissections were then performed using a modified Klingler technique to demonstrate the location of major tracts.

**RESULTS** The authors identified 3 major connections of the OFC: a bundle to the thalamus and anterior cingulate gyrus, passing inferior to the caudate and medial to the vertical fibers of the thalamic projections; a bundle to the brainstem, traveling lateral to the caudate and medial to the internal capsule; and radiations to the parietal and occipital lobes traveling with the inferior fronto-occipital fasciculus.

**CONCLUSIONS** The OFC is an important center for processing visual, spatial, and emotional information. Subtle differences in executive functioning following surgery for frontal lobe tumors may be better understood in the context of the fiber-bundle anatomy highlighted by this study.

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**KEY WORDS** orbitofrontal; ventromedial; DTI; anatomy; tractography; white matter

SINCE Brodmann first characterized the orbitofrontal cortical region in 1909,<sup>28</sup> our knowledge of the prefrontal cortex has expanded to include its role in executive behavior and cognition. As our understanding of the prefrontal cortex has increased, it has become more apparent that its dorsolateral, ventromedial, and orbitofrontal subdivisions serve specific functions.<sup>3</sup> For instance, it is clear that the orbitofrontal gyri are important in decision making.<sup>30</sup> Human neuroimaging and animal lesion studies have demonstrated that this area plays a critical role in outcome evaluation and risk assessment related to anticipating reward.<sup>16,18,30</sup>

However, an improved understanding of the role in cognition of these regions within the prefrontal cortex has yielded relatively little clinically applicable information. While speech and motor mapping have quickly become the standard for operating in speech and motor areas, it has been difficult to validate intraoperative tests for mapping regions associated with executive functioning. Adaptations of the Stroop test<sup>47</sup> have been implemented intraoperatively to address this challenge.<sup>52</sup> Although these cognitive tests may improve surgical outcomes, another key in preserving executive function is an understanding of the subcortical connections that host these critical networks.

**ABBREVIATIONS** DTI = diffusion tensor imaging; IFOF = inferior fronto-occipital fasciculus; LI = lateralization index; OFC = orbitofrontal cortex; OFG = orbitofrontal gyrus; ROI = region of interest; SFG = superior frontal gyrus.

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In this paper, we show how orbitofrontal cortex (OFC) network connectivity is organized and propose adaptations of surgical techniques to save it in relevant cases. Maintaining subcortical connectivity has been shown to decrease postoperative motor deficits in patients undergoing surgery with diffusion tensor imaging (DTI)-based neuronavigation.<sup>55</sup> Neurofunctional data has provided a basis for understanding networks involved in executive functioning,<sup>17,30,56</sup> and these principle networks rely on various orbitofrontal areas. Despite this, the surgical anatomy of orbitofrontal connectivity has not been described in neurosurgical literature. Through DTI-based fiber tracking validated by gross anatomical dissection as ground truth, we have characterized these tracts based on key connections and anatomical relationships to other structures.

## Methods

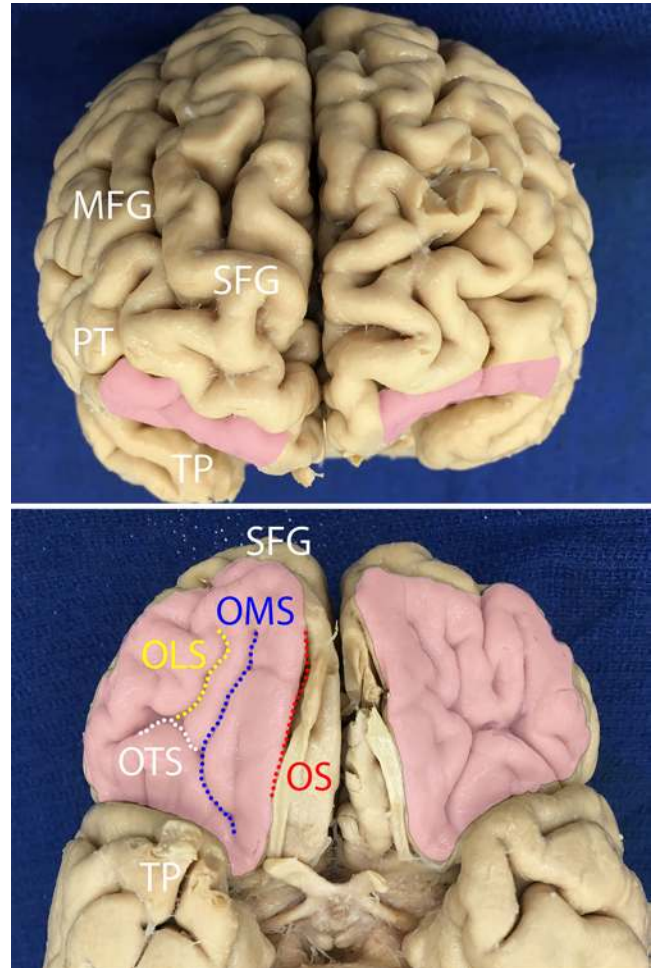
### Definition of Region of Interest

There is a degree of ambiguity with respect to terminology for prefrontal areas; this is a result of multiple disciplines studying the region. From a functional standpoint, OFC is taken to refer to frontal cortical areas involved in reward processes and decision making,<sup>20,30</sup> but from an operative perspective, distinctions based on anatomical structures are more practical. In this study, we will use gyrus-based descriptions to describe areas of connectivity. For our purposes, OFC is taken to be the anterior-most region of the cerebral cortex bounded on the posterior lateral edge by the inferior frontal gyrus (also referred to as ventrolateral cortex in functional literature<sup>37</sup>), posteriorly by the insula, and medially by the gyrus rectus. The gyri contained within the OFC are the anterior, posterior, medial, and lateral orbital gyri.<sup>42</sup> This is shown in Fig. 1.

### Tractography

Publicly available imaging data from the Human Connectome Project (HCP) was obtained for this study from the HCP database (<http://humanconnectome.org>, release Q3). Diffusion imaging from 10 healthy adult controls was analyzed. A multishell diffusion scheme was used, and the b-values were 990, 1985, and 1980 seconds/mm<sup>2</sup>. Each b-value was sampled in 90 directions. The in-plane resolution was 1.25 mm. The slice thickness was 1.25 mm. The diffusion data were reconstructed using generalized q-sampling imaging<sup>58</sup> with a diffusion sampling length ratio of 1.25.

We performed brain registration to Montreal Neurological Institute (MNI) space, wherein imaging is warped to fit a standardized brain model for comparison between subjects.<sup>4</sup> Tractography was performed in DSI Studio (Carnegie Mellon) using 2 predefined regions of interest (ROIs) to isolate single tracts.<sup>35,58</sup> Voxels within each ROI were automatically traced with randomized seeding of the voxel and/or tract with a maximum angular threshold of 45°. When a voxel was approached with no tract direction or a direction change greater than 45°, the tract was halted. Tractography was stopped after reaching a length of 450 mm. In some instances, exclusion ROIs were placed to exclude obviously spurious tracts that were not involved in the network of interest. All tracts were dissected in both hemispheres for all regions of the OFC.



**FIG. 1.** Superficial anatomy of the orbitofrontal cortex (OFC). **Upper:** The OFC lies inferior to the superior frontal gyrus (SFG) and medial frontal gyrus (MFG) and inferomedial to the pars triangularis (PT). **Lower:** Basal view of the OFC. The medial orbital gyrus is lateral to the olfactory sulcus (OS) and medial to the medial orbital sulcus (OMS, blue dotted line). The lateral orbital gyrus lies lateral to the lateral orbital sulcus (OLS, yellow dotted line) and anterolateral to the transverse orbital sulcus (OTS, white dotted line). The anterior orbital gyrus is located between the OLS and OMS. Pink indicates the OFC. TP = temporal pole.

ROIs were placed manually to isolate major tracts. Tractography was performed anteriorly to posteriorly beginning with the medial gyrus, and proceeding to the anterior, posterior, and lateral gyri. All major fiber bundles reported in this study were independently identified by a minimum of 3 investigators in all subjects studied. Tractography was completed prior to cadaveric study. The lateralization index (LI) was calculated with resultant tract volumes from major identified tracts bilaterally.<sup>50</sup> An unpaired t-test was used to assess statistical significance of any difference between these indices. A p value  $\leq 0.05$  was considered statistically significant.

### Postmortem Dissection

The purpose of the postmortem dissections was to demonstrate the location of major tracts connecting to

the orbitofrontal gyrus (OFG). Postmortem dissections were performed using a modified Klingler technique.<sup>29</sup> Ten specimens were used for this study; all specimens were obtained from our institution's Willard Body Program with approval of the state's anatomical board. The cadaveric brains were fixed in 10% formalin for at least 3 months after removal from the cranium. Up until the time of dissection, the pia-arachnoid membrane was left attached.

After fixation with formalin, specimens were rinsed with water for 2 days and then frozen at  $-10^{\circ}\text{C}$  for 8 hours, causing white matter disruption. After thawing, dissection of the "freeze-fractured" specimen began with removal of the meninges and identification of cortical anatomy, including gyri and sulci. Relevant cortical areas were identified first. Starting superficially, they were then peeled back to reveal white matter areas of interest. Care was taken to leave cortical areas corresponding to white tracts of interest intact to preserve their relationship. Tracts were dissected with blunt instruments to avoid disrupting the natural tract anatomy. Photographs were taken at each stage of the dissection.

## Results

### Connections to the Thalamus and Anterior Cingulate Gyrus

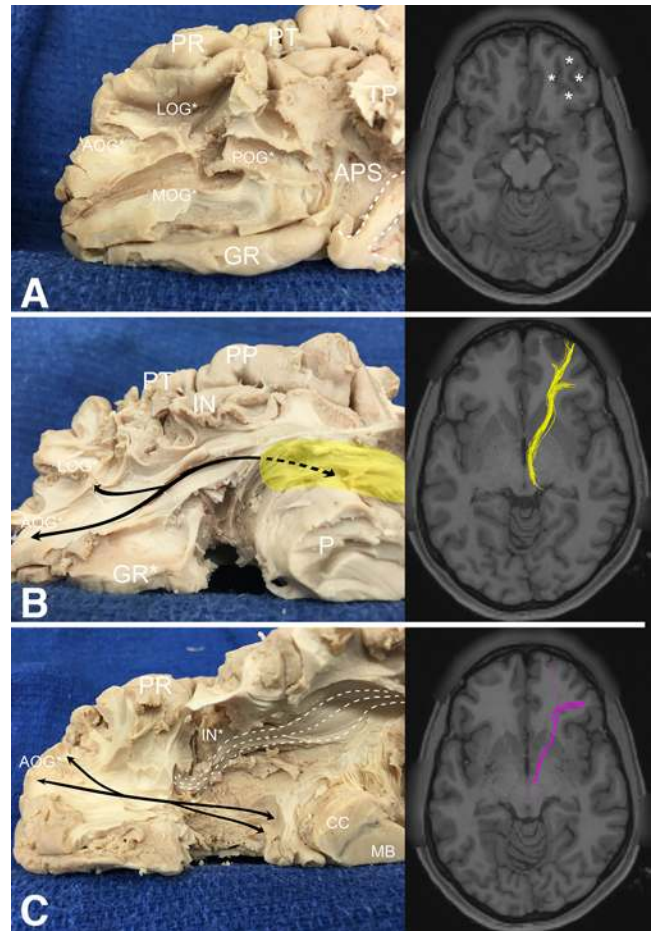
Starting from the anterior portion of the medial aspect of the hemisphere, the C-shaped cingulate sulcus is formed by the junction of the anterior cingulate gyrus and the superior frontal gyrus (SFG). A more superficial fissure divides the surface of the SFG into anterior and posterior portions. Inferiorly, the SFG is continuous with the gyrus rectus (also called the straight gyrus) along the medial edge of the hemisphere. The medial orbital gyrus rests lateral to the anterior aspect of the SFG/gyrus rectus. Fibers traversing into the superomedial portion of the thalamus pass lateral to the gyrus rectus and beneath and lateral to the caudate. Crossing fibers of the corpus callosum are superior and medial to this fiber bundle, and the vertical fibers of the thalamic projections are located laterally. Comparison with tractography with DTI is given in Fig. 2. The LI was  $-0.14$  ( $p = 0.19$ ).

### Brainstem Connections

Bundles from the orbitofrontal gyri also connect with the lateral midbrain via the cerebral crus. The tract remains lateral to the caudate and medial to the internal capsule in the entirety of its anterior-posterior course. Tractography is shown for comparison in Fig. 2 and additionally demonstrates branches to the medial and lateral aspects of the OFG. More medial fibers leaving the midbrain continue anteriorly to the medial OFG, while more lateral parts of the bundle curve laterally to the lateral OFG. However, these minor branch points were not demonstrated with *ex vivo* dissections.

### Projections to Temporal, Parietal, and Occipital Lobes

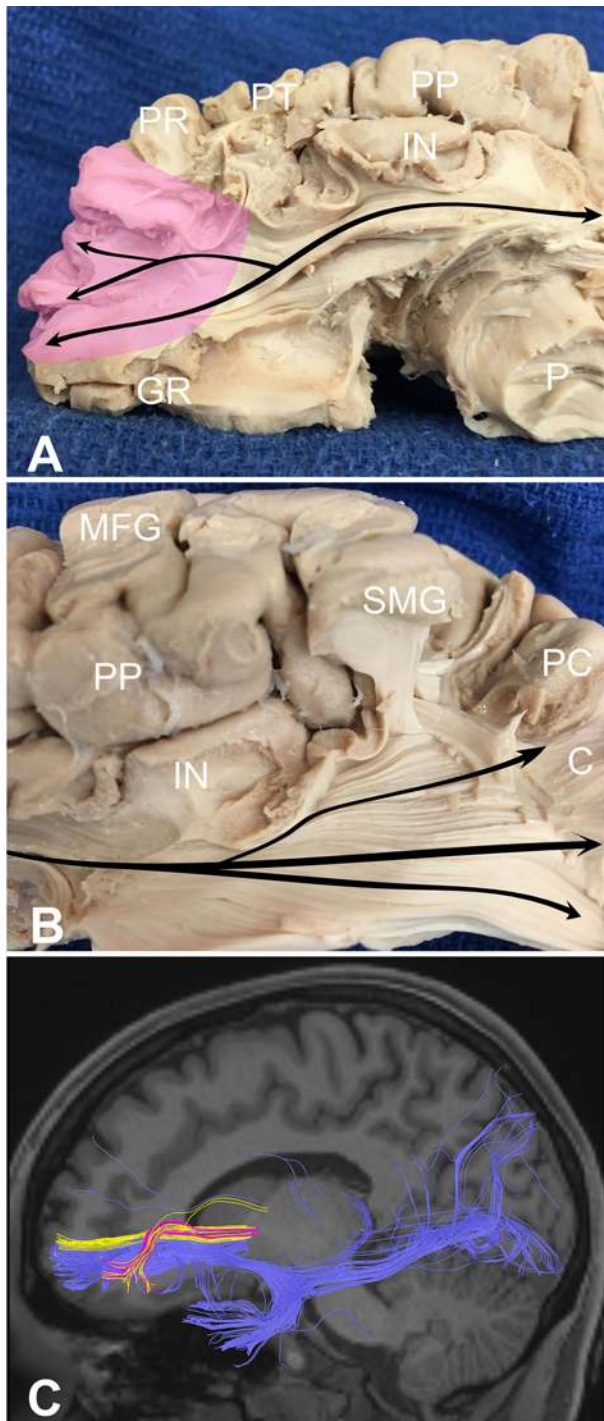
The lateral-most portion of the OFG connects to regions throughout the parietal and occipital cortex through long projections traveling with the inferior fronto-occip-



**FIG. 2.** Orbitofrontal connections to the thalamus and anterior cingulate gyrus. **A:** Blunt dissection through the anterior portion of the right hemisphere showing the orbital gyri in relation to surrounding structures and an axial T1-weighted MR image with associated asterisks denoting the areas of interest. **B:** Fiber dissection showing tracts from the orbitofrontal gyri traversing into the superomedial portion of the thalamus, passing lateral to the gyrus rectus (GR), and beneath and lateral to the caudate. Yellow indicates the orbitofrontal connection to the thalamus. Pathway shown by tractography (right) for comparison. **C:** Fiber dissection revealing path of crossing fibers of the corpus callosum that lie superior-medial to the bundle in B. Pathway illustrated by tractography for comparison. Pink indicates the crossing fibers of the corpus callosum. AOG = anterior orbital gyrus; APS = anterior parolfactory sulcus; CC = crus cerebri; IN = insula; LOG = lateral orbital gyrus; MB = midbrain; MOG = medial orbital gyrus; POG = posterior orbital gyrus; P = pons; PP = pars opercularis; PR = pars orbitalis.

ital fasciculus (IFOF). Anteriorly, the fibers joining the IFOF originate beneath and lateral to the bundles to the thalamus and brainstem. After passing beneath the limen insula, the bundle connecting to the orbitofrontal gyri divides. The majority of the fibers continue posteriorly to form connections throughout the medial and occipital cortex. Some fibers turn anteriorly with the uncinatus fasciculus to connect to anterior portions of the superior and middle temporal gyri.

Of note, fibers traveling more laterally with the IFOF continue to the occipital cortex, while fibers connecting to



**FIG. 3.** Orbitofrontal projections to temporal, parietal, and occipital lobes. **A:** Sagittal dissection through the right hemisphere; fiber dissection revealing connection to the OFG (pink). As the tract passes beneath the limen insula, the bundle connecting to the orbitofrontal gyri divides into superior and inferior tracts as it progresses anteriorly. **B:** Fiber dissection revealing continuation of posterior fibers to the medial and occipital cortex. Inferior to the insula (IN), the tracts divide into 3 main divisions as they reach the precuneus (PC) and cuneus (C) gyri. **C:** Tractography demonstrating the orientation of the fibers as they spread posteriorly and anteriorly. As the fibers progress posteriorly, some divide and turn anteriorly to connect to the superior and medial temporal gyri. SMG = supramarginal gyrus.

parietal areas course more medially. Following an imaginary line inferiorly from the marginal portion of the cingulate sulcus, which is formed by the junction of the pre-cuneus and the postcentral gyrus, the parietal projections pass medial to the superior longitudinal fasciculus. This is shown in Fig. 3.

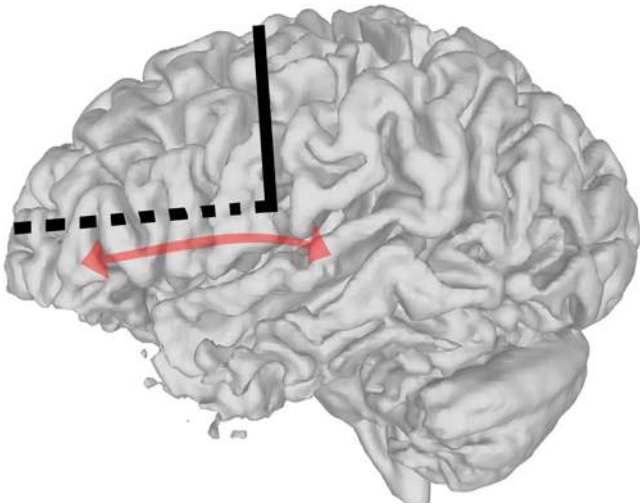
## Discussion

In this study, we address connectivity of the OFC between regions important in outcome evaluation and risk assessment. Despite the significance of these networks to daily life, to our knowledge no previous study has described the subcortical anatomy relevant to OFC surgery. The view that functional preservation in cerebral surgery depends on preserving connections between components of functional networks has become broadly accepted.<sup>15</sup> Using diffusion tractography validated by gross anatomical dissection, we describe the connections of the OFG within the context of surgical anatomy in 10 normal subjects and 10 hemispheres, respectively. We found good concordance between the two methods employed in this study, as have earlier authors.<sup>10</sup> We focus our discussion primarily on the major tracts connecting to the OFG, as these constitute the bulk of connectivity to other areas of the brain, and are large enough to be clinically actionable. These are the distinct fiber bundles connecting the OFG with the thalamus and brainstem, as well as radiations to the occipital and temporal lobes.

## Implications for Cerebral Surgery

The effect of surgery on tumors involving this network has been subtle, but apparent, in earlier studies. In a 2007 study, Szatkowska et al. described differences in patients undergoing OFC resection, reflecting the likely significance of involvement of either dominant or nondominant sides. They found that patients undergoing dominant-side resection performed worse on the Stroop test, and patients with resection of OFC on either side performed worse on the Trail Making B test.<sup>48</sup> In a 2011 study, by comparing patients with left-sided lesions to control patients and patients with right-sided OFC lesions, they showed that left-sided OFC plays a crucial role in working memory.<sup>49</sup> However, based on their results, right-sided OFC may still modulate some aspects of guiding behavior.

Additionally, patients with postsurgical, unilateral lesions to the OFC have shown deficits in facial expression identification, social behavior, and emotional state.<sup>6,23</sup> Nonsurgical lesions to the same area have led to similar results, with bilateral lesions being more dramatic.<sup>6,19,26</sup> These changes are notably occult, given the minimal changes to memory, motor function, language, and executive function.<sup>1</sup> Fitting with our understanding of OFG and emotion, patients with tumors in proximity to OFG have been observed to perform significantly worse on emotional response testing.<sup>26</sup> However, most likely due to lesser white matter tract damage, radiation does not seem to affect this network.<sup>7</sup> Additionally, fMRI studies have shown recruitment of different cortical areas during executive action in some tumor patients, suggesting that the OFG, similar to motor and speech areas,<sup>27,44</sup> has the ability to reorganize.<sup>40</sup>

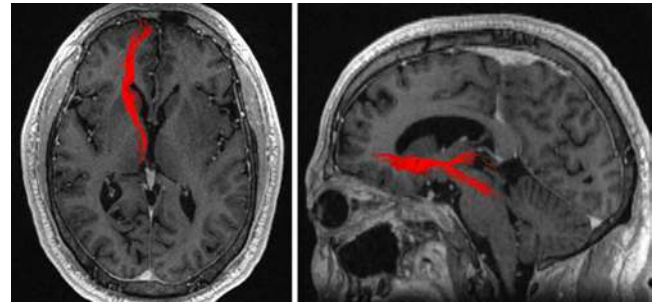


**FIG. 4.** Schematic representing a technique for preservation of orbitofrontal connectivity (*red solid line*). Tractography incorporated into image guidance and awake brain mapping are often employed during the posterior disconnection (*solid black line*) of a frontal lobectomy to preserve language functioning. Similarly, tractography with intraoperative attention testing may aid in preserving functionality of the orbitofrontal gyri during resection of the inferior aspect of the tumor (*dashed black line*).

We suggest that while OFC connectivity cannot be saved in every case, that when oncologically feasible, it should be saved because 1) it is subtly eloquent brain and OFC resection can impair function in some people, and 2) there are limited direct connections between the OFC and the rest of the brain. In presenting the connections of the OFC in their entirety, along with relevant surgical anatomy, we offer the location and nature of tracts that may be affected by frontal tumor surgery. Earlier studies have focused on functioning of the OFG or on surface anatomy,<sup>43</sup> limiting their direct utility in tumor surgery. With a working understanding of the subcortical anatomy and the location of these tracts relative to the tumor, surgeons can plan operative approaches that further minimize risk to the patient.

For instance, in a frontal lobectomy, the primary focus is on preserving anatomy associated with language, such as Broca's area and the superior longitudinal fasciculus.<sup>9</sup> These can be disrupted during the posterior disconnection of the frontal lobe. However, with awake mapping and careful operative planning with image guidance, postoperative aphasia is a rare complication.<sup>8</sup> Yet, standard intraoperative testing for frontal lobe function is not yet established. Thus, we propose limiting the inferior aspect of this cut when possible, as it may be useful in preserving salient connections of the orbitofrontal areas to the midbrain and thalamic nuclei (Fig. 4). This can be achieved using standard image-guidance platforms (Fig. 5).

One of the major challenges in highlighting the clinical implications of operating in this region has been limited availability of reproducible tests for executive function.<sup>11</sup> Contemporary neurosurgical literature has placed a heavy emphasis on outcomes with respect to survival and global functioning, without examining detailed cogni-



**FIG. 5.** Use of a standard image-guidance platform for the identification of major OFG connections. Screenshots from an MRI navigation map with tractography overlay (*red*) in the axial (*left*) and sagittal (*right*) planes demonstrate how the anatomy described in this study may be used for surgical planning. These tracts were visualized using a Stealth-Viz planning station (Medtronic) by a nonexpert in less than 5 minutes. Major fiber bundles to the thalamus and midbrain are shown.

tive status pre- and postoperatively. This currently limits conclusions that can be drawn about anatomic-functional correlates within the frontal lobe. Future work in this area may indeed be focused on improved methodologies for systematically examining patients with orbitofrontal pathology with standardized neuropsychological testing. An improved understanding from a functional standpoint will also better inform decisions regarding the limits of resection.

#### Relation of Gross Dissection to Tractography

Unsurprisingly, gross dissection did not allow visualization of every individual tract seen with tractography. Generalized q-sampling (GQI) allowed us to perform tractography in voxels that contained crossing fibers,<sup>58</sup> which was particularly useful in proximity to the brainstem. Where gross anatomical dissections allow for qualitative understanding of tract orientation, tractography allowed us to quantify tract volume to better understand laterality. In freeze-fractured brains, major tracts were clearly evident. As such, prior knowledge would have influenced DTI results to a much greater extent than findings in anatomical dissection. The results of the cadaveric study are primarily limited by the technique, which is aimed at larger, macroscopic anatomy.

The general morphology of the major tracts was constant across specimens: medial fibers of the OFG connect to the thalamus, with the fibers connecting to the brainstem coursing more laterally. Lateral and inferior to these were the radiations traveling with the IFOF, which connected to the posterolateral portion of the OFG.

#### Orbitofrontal Cortex and Sensory Processing

All functions attributed to the medial and lateral OFG require sensory input, and various models of interaction have been proposed. Previously, these projections have been noted in nonhuman primate<sup>5,12</sup> and DTI<sup>25</sup> studies. The parietal and occipital radiations noted in our tractography present a direct pathway for information from spatial and visual association cortices to reach the OFG. Given the role of the OFC in reward pathways,<sup>16,21,30</sup> connections be-

tween OFG and visual association cortex likely reinforce the positive visual identification of an object.<sup>33</sup> That is to say, during the act of visually searching for an object, the OFC is important in deciding whether the object visualized is the target.<sup>25,31,33,36</sup> This process helps explain activation of reward pathways associated with visualizing currency, which is known to play a role in gambling and other risk-based decisions.<sup>14,31,36</sup> Consequently, patients affected by tumors of the OFC can experience behavioral changes resulting from changes in perception of risk. One recent study showed that meningioma patients with tumors involving the OFC had poor postoperative scores on the Iowa Gambling Task.<sup>1</sup> Interestingly, these patients had no overall change in attention, perception, memory, language, or executive function as measured by a standardized neuropsychological evaluation.

Involvement of the OFG in reward pathways plays a role in the learning of spatial relationships through parietal connections.<sup>13,45</sup> These connections can explain why the perception of reward is proportional to an individual's distance from a target.<sup>32</sup> These relationships fit with accepted views of the OFC as a center for evaluation control.<sup>46</sup> However, this functional relationship is subtle, and it is difficult to appreciate clinically, as lesions of the parietal lobe can have countless manifestations.

### Orbitofrontal Cortex and Emotion

We elected to study the laterality of the fiber bundle connecting the OFG to the thalamus, as this connection seems to be the most critical in executive functioning. Proximal connections between the thalamus and OFC and the anterior cingulate and OFC have been the subject of many animal studies.<sup>2,21,24</sup> These connections have been extensively linked to cognition, memory, and emotion.<sup>5</sup> Projections from the mediodorsal thalamus in particular have an established role in emotion and reward linked to decision making.<sup>39</sup> These tracts have been studied in a number of psychological processes.<sup>51,53,54</sup> Well-known examples include a link between treating epilepsy of the OFC and reversible antisocial behavior.<sup>51</sup> There is also a link between schizophrenia and tract abnormalities connecting the OFC to the anterior cingulate cortex.<sup>38,46,53</sup> Many behavioral/emotional disturbances make sense within the context of the OFC as important for evaluation control.<sup>46</sup>

As a whole, this network has been used in the treatment of several conditions. For instance, disconnecting tracts from the thalamus to the OFC has been successful in treating obsessive-compulsive disorder (OCD) with subcaudate tractotomy.<sup>22,57</sup> Deep brain stimulation has also been successful in treating OCD,<sup>41</sup> likely by acting on connections of the OFC to the thalamus in the ventral capsule/ventral striatum region.<sup>34</sup>

### Conclusions

The OFG is an important center for processing visual, spatial, and emotional information. Subtle differences in executive functioning following surgery for frontal lobe tumors may be better understood in the context of the fiber-bundle anatomy highlighted by this study.

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### Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

### Author Contributions

Conception and design: Sughrue, Burks, Bonney. Acquisition of data: Burks, Conner, O'Donoghue, Wu. Analysis and interpretation of data: Burks, Conner, O'Donoghue, Wu. Drafting the article: Sughrue, Burks, Conner, Bonney, Glenn, Boettcher. Critically revising the article: Sughrue, Burks, Glenn, Baker, Boettcher, Briggs. Reviewed submitted version of manuscript: Baker. Administrative/technical/material support: Sughrue, Baker.

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