

# Keynote Address: Revaluating the Orbital Prefrontal Cortex

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**ABSTRACT:** The importance of orbitofrontal cortex (OFC) in human behavioral regulation is no longer a matter of dispute, though its precise role remains a matter of ongoing investigation. It is ironic that this revaluation of OFC required a major departure from a historical nadir, during which it was viewed as redundant or “silent cortex,” a situation that prevailed even up to the latter half of the 20th century. The increasing wealth of data from diverse fields within neuroscience now provides an unambiguous testament to the importance of this cortical region in behavioral regulation and cognition in general.

**KEYWORDS:** OFC; lobotomy; value

## INTRODUCTION

Historically, the lowly status the orbitofrontal cortex (OFC) can be traced back to the 18th century, when the British surgeon Percivall Pott (1713–1788) (who it turns out provided the first account of an environmental basis to cancer, describing scrotal cancer in chimney sweeps), gave expression to what would become a prevailing view. Pott suggested that a brain injury “in or under the frontal bone” was of much less consequence than intracranial damage in any other location. He noted, “I will not assert it to be a general fact, but as far as my own experience and observation go, I think that I have seen more patients get well, whose injuries have been in or under the frontal bone, than any other bones of the cranium. If this should be found to be generally true, may not the reason be worth enquiring into.”<sup>1</sup> One hundred years later, John Harlow, who documented the tragic fate of Phineas Gage, may well have been articulating what had become canonical medical lore when he asserted that the sector brain traversed by the tamping iron was “the best fitted of any . . . to sustain the injury.”<sup>2,3</sup>

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## PSYCHOSURGERY

The lowly status attributed to OFC found an institutional expression with the birth, and widespread tolerance, of psychosurgical lobotomy in the treatment of psychiatric disorders. It is hard to imagine that this practice would have been tolerated had this cortical region been ascribed any reasonably defined function. Cynically, one might conclude that an unchartered sector of brain is as vulnerable as uninhabited patches of earth, ripe for exploitation by the unscrupulous. Apologists for this form of medical intervention have argued that psychosurgery provided relief in an era that preceded the psychopharmacological revolution.<sup>4</sup>

Psychosurgery, a dominant and dramatic form of treatment in psychiatry between the 1940s and the 1960s, was developed by Egas Moniz. Moniz was Professor of Neurology, in Lisbon, Portugal. He became aware of the potential effects of ablation of prefrontal cortex in 1935 when, at a conference in London, he heard a description of the effects on chimpanzees who had ablations to their prefrontal cortex. What grabbed his attention was an observation that one of the animals was apparently “cured” of an “experimental neurosis.” The “experimental neurosis” in this case was nothing short of temper tantrums in an animal who was a subject in experiments designed to assess the contribution of the frontal lobes to performance of a delayed-response task. This anecdotal report of the effects of experimental training on a single animal was enough to spur Moniz who, in collaboration with his neurosurgical colleague, Almeida Lima, introduced the technique known as pre-frontal leukotomy just 1 year later. Moniz was not unaware of widespread skepticism in relation to the procedure. Quoting a colleague, he liked to assert that “the indignation of those who oppose lobotomy tests rests in the subconscious conviction that the removal of a part of the brain robs a man of part of his soul.”<sup>5</sup>

The procedure preferred by Moniz’s surgeon Almeida Lima (1903–1985) involved using an instrument called a leukotome, which was passed into the frontal white matter via burr holes drilled into the vertex of the skull above each frontal lobe. The tip of the leukotome contained a wire loop, which when extended and rotated resulted in a core of tissue being disconnected from the surrounding white matter. Moniz and Lima (1936) published on 20 patients submitted to this new technique, that conformed to the rule of thirds: 7 were considered cured, 7 improved significantly, and 6 were unchanged.<sup>6</sup> The immediate impact of leukotomy can be gauged from the fact that Moniz was awarded the Nobel Prize in Medicine in 1949 for pioneering the development of the technique.

## PSYCHOSURGERY AND PSYCHIATRY

Psychosurgery might have been confined to the dustbin of heroic psychiatric practices were it not for the Pauline proselytizing zeal of Walter Freeman, an

American neurologist. In collaboration with his neurosurgical colleague James Watts, he introduced a technique that involved making a cut to the entire white matter of the frontal lobes, his so-called standard lobotomy. At a time where empirical evidence had a low premium, it was often the character of a practitioner that determined the acceptance of a medical treatment. Freeman might reasonably be inferred to have expressed a low risk aversion and indeed, prior to embarking on leukotomy, he had developed a rapid procedure for obtaining a spinal fluid which he referred to as “my jiffy spinal tap,” which involved inserting a needle through the foramen magnum into the cisterna magna.<sup>7</sup>

Nor surprisingly, Freeman was interested in a rapid lobotomy technique, and this led him to develop what came to be known as the trans-orbital lobotomy, a procedure that involved gaining access to the frontal lobes by driving an instrument that was akin to an ice-pick behind the eyeballs, passing through the orbital roof, and then cutting the white matter. Here the procedure primarily targeted the connections between the OFC and the rest of the brain. What is now shocking to learn is that Freeman carried out his early operations not in an operating theater, but in his office and was not averse to operating on the those unwilling, or indeed incapable, to give consent. A single operating session might involve performing lobotomies on up to 20 patients, which in practice meant taking no more than 10 min per patient. His most famous patient (operated upon by James Watts) was Rosemary Kennedy, the sister of the future President. During the procedure, performed following administration of a mild tranquilizer he asked her to recite “God Bless America.”<sup>7</sup>

Freeman performed his last lobotomy in Berkeley, California, in February 1967 at the age of 72. Throughout his career he continued to advocate lobotomy in the face of all evidence against its effectiveness. Any scientific justification for the procedure remained opaque, though Freeman subscribed to a view that consciousness is mediated by the frontal lobes but added that “we believe there can be too much of a good thing.” He suggested its contribution to consciousness is its ability to project an image of the individual into the future coupled with a recognition of this image as the self. A second contribution of the frontal lobes, he asserted, was in providing an “affective facet, the emotional charge connected with that image.” At his most articulate, he ascribed to a view that the prefrontal lobotomy acts specifically by reducing the affective component of the image as self as constructed by the frontal lobes, a justification succinctly summed up in his comment, one assumes drawn from anecdotal observation, that “prefrontal lobotomy bleaches the affective component connected with the consciousness of the self.”<sup>8</sup>

The shame of the tolerance of lobotomy extends beyond the undoubted harm done to the vulnerable and ill and their undoubtedly disappointed families and loved ones. It indicts, in particular, regulatory authorities who tolerated an extreme procedure for which there was a clear lack of scientific justification, let alone evidence of therapeutic efficacy. Needless to say, there has never

been much in the way of systematic evaluation of the effects on cognition of lobotomy, though a notable exception are studies by Stuss *et al.*<sup>9–13</sup>

The era of psychosurgery raises important questions in relation to current interest in the functions of the OFC. Why, if we now assume the OFC is pivotal for human behavioral regulation, were seriously damaging consequences not evident in the thousands of patients subjected to this procedure? One obvious argument might be that its negative effects were masked by virtue of the procedure being inflicted on the mentally ill. I would suggest there was a deeper reason, and this relates to what we now recognize as one of the core functions of OFC, namely in value representation. Historically, psychiatry and neurology, and to a lesser degree psychology, all have had a conceptual difficulty in accepting that subtle aspects of human behavioral regulation and character, including that encompassing the domain of moral behavior, might have a major physiological basis.<sup>14</sup>

### REASSESSING THE ROLE OF OFC

Harlow's detailed account of Phineas Gage is widely viewed as the first detailed description of brain injury resulting in a change of character. However, it is almost certainly the case that the problem of acquired character change consequent upon brain damage was already recognized as a source of burden to society. For example, take a 16th century account, from William Shakespeare's Stratford-upon-Avon, of a petition raised requesting that the town be "eased of the charge of one Lewis Gilbert, a maimed soldier in Ireland." Before serving in an Elizabethan military expedition to quell unrest in Ireland, Gilbert was an upstanding member of society who worked as a butcher.<sup>15</sup> On his return he became a public burden being accused of forcible entry, failure to pay debts, and finally stabbing a neighbor to death in a quarrel. Although we have no detail of his actual injury, it is striking that the petition focuses entirely on behavioral changes rather than any physical deformity and implicitly endorses a lack of culpability on his behalf in relation to his misdemeanors and indeed a murder attributed to him.

The highly documented and famous case of Phineas Gage has now been the subject of countless descriptions. It is worth pointing out one class of problem that seems especially relevant to our contemporary understanding of the role of OFC. This is seen in Harlow's observation that his patient "does not estimate size or money accurately, although he has memory as perfect as ever. He would not take \$1000 for a few pebbles which he took from an ancient river bed where he was at work." He goes on to describe that he "purchased some articles at the store, enquired to the price, and paid the money with his habitual accuracy; did not appear to be particular as to the price, provided he had money to meet."<sup>16</sup> This description seems particularly pertinent to views that the OFC contributes to valuation, including abstract valuation.

## THE REDISCOVERY OF THE OFC

The first half of the 20th century was not without figureheads who recognized the importance of the orbital prefrontal cortex. Alexander Luria, in his book *Higher Cortical Functions in Man* (1980), noted that clinical observation pointed to the fact that no sensory or motor effects arise consequent upon electrical stimulation in the frontal lobes. He noted also that massive lesions of the frontal lobes are unaccompanied by obvious disturbances of visual, auditory, or tactile sensations, or indeed any disturbance of movement. He strongly refuted any conclusion that might seem to logically ensue from such observation, namely that the frontal lobes have no clearly defined function and must, in keeping with prevailing views, be regarded as “silent zones” of cortex. Instead, he noted that “careful observation of complex forms of animal behavior and, in particular, complex forms of human conscious activity lead to completely different conclusions regarding the function of the frontal lobes.”<sup>17</sup>

Luria noted that almost all patients with lesions of the frontal lobe lose a “critical faculty” by which he meant an ability to evaluate behavior and the adequacy of actions. He characterized different variants of frontal lobe syndrome based upon an anatomical differentiation. For example, he observed that damage or pathology to the frontal lobes that involves the basal division results in a tendency toward impulsive action, trivial jokes, and euphoria without significant change in intelligence. Furthermore, with lesions to this sector he observed that the syndrome profile shifts towards affective disturbance leading to disturbance of character and personality.<sup>17</sup>

It is important to mention two other key figures who recognized the importance of the OFC, Karl Pribram and William Nauta. Pribram reported that with ablation of prefrontal cortex, reinforcement of motor reactions in a choice situation did not bring about the predicted change in an animal’s behavior. In seminal observations, which anticipated reinforcement learning accounts of action learning, he concluded that disregard for the effect of one’s own movement, which he referred to as a success signal or mistake signal, is an essential sign of disturbed behavior consequent upon resection of the frontal lobes.<sup>18</sup> In simple terms Pribram appears to have here captured the idea that a discrepancy between an intention and an outcome, that might be thought of as a prediction error, was no longer expressed in the context of OFC damage.

Nauta highlighted a putative role of OFC in affective guidance of decision making.<sup>19</sup> He suggested that when an individual embarks on a course of action that involves a choice between alternatives, the choice is likely to be strongly determined by a comparison of the affective responses evoked by each of the alternatives. He commented that “if this were indeed the case, it would be readily understandable that loss of frontal cortex as a major mediator of information exchange between cerebral cortex and the limbic system is followed not only by an impairment of strategic choice making, but also by

a tendency of projected or current action systems to ‘fade out’ or become over-ridden by interfering influences.”

A landmark account of the role of OFC in behavioral regulation is the clinical paper of Eslinger and Damasio.<sup>20</sup> Their patient, EVR, following resection of an orbitofrontal meningioma, acquired a profound impairment in his ability to make advantageous choices, both in his personal and social life. EVR was described as “not spontaneously motivated for action. He seemed not to have available, automatically, programs of actions capable of driving him to motion.” The authors noted that while damage to OFC may not impact on intellectual function, as ascertained in classical tests of intelligence, it does impact on subtle components of behavioral regulation. Thus, the most striking observation was the dissociation between intact cognitive abilities measured in standardized tests and poor utilization of these abilities in real-world environments. The core observation in this single case study has been widely replicated. In a detailed analysis of a large cohort of patients with brain injury, including a large cohort with frontal injuries, it was noted that with ventro-medial prefrontal cortex (VMPFC) damage the most common symptoms include blunted emotional experience, poorly modulated emotional responses, defective social decision making, impaired goal directed behavior, and lack of insight.<sup>21</sup>

## THE SOMATIC MARKER HYPOTHESIS

An important theory to emerge out of renewed interest in the behavioral effects of damage to OFC, particularly the VMPFC sector, is the somatic marker hypothesis. A basic premise of this hypothesis is that visceral sensory signals are mapped in OFC. As a consequence, patients with damage to VMPFC make poor decisions partly because they do not elicit somatic responses that index the consequences of their actions as positive or negative. In simple terms the theory proposes that VMPFC elicits visceral responses that reflect the anticipated value of future choices, a process that is enhanced under decision making under uncertainty. Decision making under uncertainty is thus seen as eliciting gut feelings or hunches that inform or bias decision making based upon a forward model.

The idea of guidance of behavior on the basis of future likelihood of reward or punishment, as suggested in the somatic marker hypothesis, is an idea captured within the formalism of reinforcement learning theory of the likely consequences of decision options.<sup>22</sup> Reinforcement learning in its simplest form encapsulates the problem faced by an agent who learns, not by instruction, but through trial-and-error interactions within an environment. The key idea is that under conditions of uncertainty, as in unsupervised settings, learning is driven by a prediction error signal. There is now good evidence that encoding

of a prediction error signal for reward is expressed within the OFC, among other regions.<sup>23</sup>

The other key clinical area that has transformed our understanding of OFC is the demarcation of a group of conditions often known as fronto-temporal dementias. These conditions represent a spectrum of disorders in which the brunt of the pathology is expressed in ventral prefrontal cortex and anterior temporal lobes.<sup>24</sup> Descriptions of patients with these conditions indicate that disturbance of emotion and behavior dominate the clinical picture, particularly in early stages, and overshadow any deficits in intellectual function. Among the most frequently noted deficits are disturbances of eating habits often associated with increased acquisition of preferences for sweet foods and lack of satiety, again reflecting problems in value representation in the broad sense.

## CONTEMPORARY PERSPECTIVES ON THE ROLE OF OFC

The shift in view regarding the role of the OFC, initially brought about by clinical observation, has led to an ever-increasing interest in defining the behavioral affiliations of this cortical region. Consequently, the OFC is now a prime focus for investigators whose approaches subsume electrophysiology, classical lesion deficit models, neuropsychology, behavioral economics, and functional neuroimaging, to mention a few. One common theme to emerge from these diverse approaches is that this structure is critical to an ability to flexibly represent and update the value of stimuli or states that contribute to long-term behavioral guidance. In this frame of reference, value representation guides behavior by indexing whether options for action are likely to be associated with reward or punishment, not only in the short term but also in the long term. This is nicely encapsulated in the suggestion that OFC is critical for integrating the incentive value of outcomes with predictive cues in the service of behavioral guidance.<sup>25</sup>

Many issues remain regarding the role of OFC, including a key issue of functional specialization, its relative contribution to affect as opposed to cognition, the specification of its precise role in behavioral guidance, the control influences it exerts over more remote structures in emotional regulation, and how neuromodulatory systems bias key functions implemented in this region. At a more clinical level, it seems likely that OFC has a key role in expression of a range of psychopathologies where, as indeed we know to be the case for OFC, there is no primary deficit in intellectual function but major deficits in motivation and behavioral control. Examples here include clinical depression, but also conditions such as psychopathy, obsessive compulsive disorder, addictive behavior, and attention deficit disorders. What no longer seems preposterous, to reprise Moniz, is the idea that that damage to the OFC might indeed rob a person of their very soul.

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