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REVIEW ARTICLE

The prefrontal cortex and neurosurgical treatment for intractable OCD

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Over the past two decades, circuit-based neurosurgical procedures have gained increasing acceptance as a safe and efficacious approach to the treatment of the intractable obsessive-compulsive disorder (OCD). Lesions and deep brain stimulation (DBS) of the longitudinal corticofugal white matter tracts connecting the prefrontal cortex with the striatum, thalamus, subthalamic nucleus (STN), and brainstem implicate orbitofrontal, medial prefrontal, frontopolar, and ventrolateral cortical networks in the symptoms underlying OCD. The highly parallel distributed nature of these networks may explain the relative lack of adverse effects observed following surgery. Additional pre-post studies of cognitive tasks in more surgical patients are needed to confirm the role of these networks in OCD and to define therapeutic responses to surgical intervention.

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a common, persistent, and oftentimes disabling disorder marked by unwanted and distressing thoughts (obsessions) and irresistible repetitive behaviors (compulsions) [1, 2]. OCD affects 2–3% of the US population [3] and is responsible for substantial functional impairment [4] and increased risk of early mortality [5]. The only established first-line treatments for OCD are cognitive-behavioral therapy with exposure/response prevention (ERP) [6] and serotonin reuptake inhibitor medications (SRIs) [7–11]. Approximately 30–40% of patients fail to respond to either modality [12, 13], few patients experience complete symptom resolution [14], up to 25% of patients have difficulty tolerating CBT [15], and the risk of relapse after therapies remains significant. Non-invasive devices like repetitive transcranial magnetic stimulation (TMS) are showing promise in non-treatment-resistant OCD [16, 17]. Adjunctive antipsychotics may be beneficial in SRI partial responders, especially those with concomitant tics [18]. However, for the most severe and refractory cases, ablative neurosurgery, either cingulotomy [19–21] or anterior capsulotomy [22–24] has long been the option of last resort.

The overall goal of this paper is to review how neurosurgical procedures for OCD have contributed to our understanding of prefrontal cortical function in health and disease. This review examines two main bodies of evidence: (1) findings from lesion studies and (2) more recent findings from neurostimulation and recording. While these studies were all designed to develop novel approaches to treatment for patients with intractable neuropsychiatric conditions, they also offered an unparalleled opportunity to study the effects of standardized brain lesions or neurostimulation on brain function. Advances in neurosurgical approaches to targeting, including structural and functional imaging and the development of new devices, have opened up the possibility of

greater precision as well as closed-loop approaches to treatment. Research over the next decade brings the promise of more effective and individualized treatments, as well as growth in our understanding of prefrontal cortical function in humans.

NEUROCIRCUITRY OF OCD

Converging data—from studies of brain imaging, cognitive-affective neuroscience, neuromodulation, and animal models—suggests that OCD represents a model neural network-based disorder [25, 26] involving dysregulation of cortico-striato-thalamocortical (CSTC) loops. Both positron emission tomography (PET) [27] and functional magnetic resonance imaging (fMRI) [28, 29] studies have shown increased activation in regions of the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and portions of the basal ganglia in the symptomatic state compared to healthy controls. These areas of abnormal activation tend to normalize following successful treatment with either pharma-cotherapy or behavioral therapy [30, 31]. Successful treatment of OCD with deep brain stimulation (DBS) [32, 33], surgical ablation [34, 35], and TMS [16, 36] has also been associated with reductions in brain activity compared to baseline. It should be noted that most of the functional imaging studies of OCD as well as imaging and electrophysiologic studies of patients who have had neurosurgical procedures have come from small studies that would not hold up to modern standards or rigorous analysis, though the findings have been replicated by many investigators in multiple sites.

An important development in circuit-based theories of OCD has been a shift in focus from static regions of interest to investigation of functional networks underpinning different cognitive or behavioral functions related to the symptoms of OCD [37–44]. The seminal contributions by Alexander et al. [45] led OCD

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researchers to examine certain parallel segregated CSTC loops, subserving different motor or cognitive functions, as the neuroanatomical basis for obsessive-compulsive behavior [30]. The standard model of a CSTC loop consists of projections from a specific region of the frontal cortex that terminate in the striatum, and then travel by either a direct (net excitatory) or indirect (net inhibitory) pathway through the basal ganglia to the thalamus, and finally returning via recurrent projections to the same cortical region to close the loop [46]. Revisions to this model reveal a more complex picture of the organization of CSTC loops [27], showing more overlap and functional integration between loops than previously appreciated as well as pointing out the importance of other interconnected structures such as the amygdala [47].

Several research groups have proposed that increased tone in the direct pathway (relative to the indirect pathway) might explain some of the neuroimaging findings and phenomenological features of OCD [30, 48]. According to this model, such an imbalance in activity between these pathways would bias the individual to the selection of, and failure to inhibit, abnormal and repetitive behavioral sequences [49]. Hyperactivity of orbitofrontal-subcortical pathways has been found in both human imaging studies in OCD and mouse models of OCD-like behaviors [48]. An influential study by Ahmari et al. [50] used optogenetics in mice to test the effects of CSTC hyperactivation on behavior. Repeated stimulation (over multiple days) of OFC-ventral striatum (VS) projections induced increased grooming behaviors, which persisted after stimulation cessation.

Chronic administration of fluoxetine reversed the aberrant grooming.

These data provide support for the role of OFC hyperactivity in the genesis of abnormal repetitive behaviors. Together, converging lines of clinical and preclinical evidence suggests that OCD involves dysfunction of limbic CTSC loops that include the OFC, vmPFC, ATI, and VS [48] It should be noted, however, that a similar study in rats failed to induce compulsive behavior following repeated optogenetic stimulation of the OFC-VS pathway [51]. This failure to replicate the Ahmari et al. study raises questions about translating the findings from mice to higher-level species.

NEUROSURGICAL APPROACHES TO OCD AND THE FRONTAL LOBES: LESIONS PREFRONTAL LOBOTOMY AND LEUCOTOMY
The history and legacy of the development of prefrontal lobotomy by the Nobel Laureate Albert Moniz, subsequently put into widespread practice by Freeman and Watts, has been well documented [52]. In contrast, the extensive literature on the effects of the procedure on behavior and the rigorous studies that attempted to correlate neuropathologic examination of the placement and size of the lesions with therapeutic outcomes [53–56] as well as the correlation of adverse behavioral effects with frontal lobe function have received less attention. These empirical studies, conducted on hundreds of patients, as well as subsequent studies on stereotactic procedures that were developed to minimize adverse effects of prefrontal lobotomy or leucotomy on personality, resulted in a rich collection of clinical observations. These studies can now be reinterpreted in light of recent findings of prefrontal cortical function, summarized elsewhere in this issue. In this section, we will attempt to explore findings from lesion studies that help shine a unique light on the function of the human prefrontal cortex. It is important to recognize the context in which Moniz developed his Nobel Prize-winning procedure in the 1930s [57]. Psychotic patients were committed to state institutions with often deplorable living conditions at an early age. Many spent decades; if not their entire lives in backward institutions with no hope of release. There was no effective antipsychotic medications available and prolonged restraint was often necessary. No wonder that a surgical procedure that radically reduced violent psychotic episodes, and

that allowed two-thirds of patients who were operated on an opportunity to return to live with their families and to work at a paying job, was initially seen as a major scientific advance. Furthermore, several well-documented reports [58–60] showed no adverse effects on intelligence or other measures of neuropsychological function at the time, prompting one author to say "*It appears that posterior to Area 6 is the part of the brain that we'll really test in determining the intelligence quotient. This is one kind of knowledge, the ability to gather facts and have them in your brain. Another kind of knowledge is what to do with these facts and it seems to me that resides in the area anterior to Area 6.*" [60] Severely disturbed schizophrenic patients became calmer, suffered less, and were easier to take care of in a home environment. The severe anxiety associated with OCD and involuntary depressive patients was relieved.

The procedure was intended to cut the connections from the frontal cortex to the thalamus and other subcortical structures. However, Freeman noted the differences between leucotomy and lobotomy, presaging the notion of the highly distributed network dynamics of the frontal lobe.

"*It would appear that the frontal cortex is isolated from the thalamus and no longer receives thalamic input except by indirect means. It appears that whatever organized activity is present in the frontal lobes has to find its expression by somewhat devious routes since the direct pathways are severed. No doubt these pathways are developed to some degree with the passage of time since patients with lobotomies often are capable of excellent social and working adjustments whereas patients with bifrontal lobectomies are permanently crippled.*" [59].

The typical procedure was carried out by quadrantal sweeps of a leucotome, introduced through lateral burr holes placed anterior to the coronal suture, through the substance of the white matter connecting the frontal lobes with the rest of the brain. Patients were operated on while awake "*On a number of occasions flattening of affect and disorientation did not appear until stab incisions were made in the depths of the quadratic sweeping incisions. In some cases it seemed as though a certain relatively small bundle of fibers was preserving the patients contact with reality and when this was sectioned the patient drifted off into confusion and unresponsiveness. As close as can be judged, the bundle is located close to the midline at about the level of the genu of the corpus callosum*" [59]. While highlighting the important role of disrupting midline connections in the outcome of the procedure, they also were pointing out that function was preserved until over 75% of the connections were severed. Rylander [61] noted: "*Discussion with patients undergoing lobotomy using local anesthesia reveals no changes after the incisions in the frontal lobe are completed on either side, or after incisions are made symmetrically in both upper halves or both lower halves of the two frontal lobes. When the third quadrant is sectioned there is a notable falling off in the length of the replies and in the display of emotion connected to them. When questioned they may upon request recite well known verses, say prayers, sing etc. but evidence no spontaneous speech. When the fourth quadrant is sectioned the patient becomes unresponsive except to urgent questions, his replies are often monosyllabic, his face is expressionless and his orientation is lost. Any preexisting nervous tension is lost with corresponding effects on pulse rate and blood pressure.*" In the discussion, Rylander goes on to describe a scrupulous woman who during her many years in the hospital was incessantly obsessing about her sins committed against the Holy Ghost. After sectioning three quadrants she continued to pray but on the section of the fourth quadrant when asked about her concerns about the Holy Ghost, she replied "Oh, the Holy Ghost; there is no Holy Ghost." On follow-up, she had lost her scrupulous tendencies and compulsive praying

Post mortem neuropathological examination revealed significant variability in the size and location of the lesions but Freeman pointed out the correlation between the extent of damage and

treatment outcome. *"There is a quantitative relationship between the amount of frontal lobe disconnected from the rest of the brain and the effects in terms of both clinical result and of personality integration. We have observed that incisions placed too far anterior of the coronal suture or at insufficient depth result in very little alteration of the patient's emotional attitude or his overt behavior. When the plane of the section is further back but still somewhat in advance of the coronal* suture *the postoperative course is characterized by euphoria, talkativeness and exuberance. This state soon gives way to a normal appreciation of self and surroundings and usually to a return of the former disabling mental symptoms. On the other hand, when the incisions in the frontal lobes are made behind the optimal plane there is always profound and prolonged depression in the individual's awareness followed by persistent vacuous euphoria and inertia."* [59] In a long-term 20-year follow-up of motor deficits in leucotomies schizophrenic patients, Benson and Stuss [53] found no signs of praxis, no elementary motor dysfunction, and no frontal release signs. Schizophrenics with the largest prefrontal damage by structural imaging learned and performed a three-step sequence task better than schizophrenic subjects with less or no bifrontal damage and as well as controls. Most of the subjects with sizeable bifrontal damage could complete going no go and alternation of response tests as well as normal controls. Careful studies that correlated lesion size and placement with treatment outcome began to point to the medial aspect of the lesion as being most critical. The lack of apparent side effects of the uncomplicated procedure in early reports was unexpected and striking. Proving that adverse neuropsychological effects occurred following the procedure was complicated by the fact that most of the surgeries were performed on schizophrenics, whose symptoms often significantly improved with the procedure masking post-operative adverse effects. Careful examination of the effects of the procedure on patients' personalities was documented 10 years later [61] but was not enough to delay widespread implementation of frontal leucotomies or orbital undercutting prior to the arrival of antipsychotic drugs in the early 1950s.

Patients suffering from severe obsessive neurosis tended to have much better therapeutic outcomes compared to schizophrenics [59, 60]. Freeman and Watts described a typical response of the OCD patient in these terms, *"There was a woman who for some thirty years had suffered from obsessive fear of contamination and who had scrubbed not only the toilet seat but the whole bathroom for an hour or so before using the toilet and then for an hour or more afterward in an effort to spare others from the danger of contamination. Following her operation, for a long period this woman manifested the same tendency toward compulsive cleaning of the bathroom before and after evaluation even though she admitted she did not feel the same anxiety and fear of contaminating others that had been previously present. The compulsive activity gradually disappeared during the ensuing years."* [59]. In order to more closely observe potential adverse effects of the procedure, Rylander began an intensive, painstaking study of severe obsessives, who had less impairment in premorbid personality structure than the schizophrenics [61]. He observed that often function was restored to the preoperative level at 4–6 months. Subtraction of serial sevens was normal after one month. Memory was intact after a lapse of two months but a striking change was seen in word enumeration (verbal fluency), a task that required naming as many nouns as possible during 3 min with eyes closed, and that did not change at long term follow-up. There was also consistent pre to post-op differences in concrete interpretations of proverbs in the OCD patients. He was among the first to report that *"a slight but fateful intellectual reduction was caused that was difficult to demonstrate with ordinary intelligence tests but that affected abstract reasoning and the ability to plan. There was a flattening of affect with a tendency toward euphoric reactions."* In Rylander's monograph of the effects of prefrontal leucotomy on

personality, he states "the operation is performed in order to change the depressed, introverted, self-occupied patients into slightly euphoric, extraverted, easy-going persons" He describes tactlessness, emotional lability, extrovertness and slight euphoric traits as characteristic changes that appeared following the procedure [61]. His case histories are illustrative of the significant but often overlooked adverse effects on personality.

"He studied Marx, Upton Sinclair, Kafka before the operation. Since lobotomy he has not read a single book of the type mentioned. His social and political interests have entirely disappeared."

"She had been a conscientious and extremely efficient operating room nurse. She has lost much of her ambition, her interest in work and particularly her sympathy with the patients. Her attitude now…I don't care if I make a mistake… it will turn out alright in the end… is opposite of that before the operation."

"This patient had loved classical music before the operation….now she only cares for dance tunes. Before she was religiously inclined… now she thinks religion is humbug. Originally she was a clever cook…now she has difficulty using new recipes and makes ridiculous errors, but her old cooking recipes she made faultlessly. Going out to buy food, she might disappear for half a day, forgetting her time and duties. She has real difficulty in seeing the possibility that there is more than one solution to a problem."

Robinson [62] pointed to deficits in goal-directed behavior and planning in action and in speech as well as agency: *"They show the traits characterized by Freeman and Watts as a shift from introversion to extraversion, exhibiting cheerfulness, decreased self-consciousness and lack of prudence. Their conversation tends to slip readily from one subject to another. They have become not so much social as gregarious, not more interested in the thoughts of others merely less in their own. They have no hint of ulterior motives. Past and future seem telescoped into the present. It is the capacity for deliberateness that they have missing."*

Freeman and Watts pointed to the role of the frontal cortex in social interaction and anxiety, delayed discounting as well as its role in projecting the image of the self into the future [59]. *"The frontal lobes are important for insight, for subtlety, for postponing pleasure and for projecting the individual self into the future. They are essential for the elaboration of a vivid picture of the future with all its deviations all its implications all its difficulties and dangers all its triumphs and disasters…the operated patient lives in a perpetual present, his interests in the outside world being much more vivid than his interests and reactions to them."* *"The outstanding feature in social interaction is the lack of self-consciousness. They cannot be insulted. They do not take offense; life is enormously simplified by the relatively complete obliteration of the need for introspection"*

Finally, Freeman and Watts pointed to the importance of the reduction of the anticipatory anxiety linked to an obsession in therapeutic outcome

"We have compared the emotion to the fixing agent that prevents a photographic image from fading back into obscurity. Remove the emotion and the image gradually fades. Prefrontal lobotomy bleaches the affect attached to the ego……in the obsessive state prefrontal lobotomy reduces or abolishes the feeling tone attached to the obsessional ideas. The ideas continue and the compulsions often last a long time but the anxiety or tension associated with them is no longer present. One patient said it is as though the painful idea which used to be in the center of the circle of my attention has receded to the periphery."

There is an interesting parallel between the subjective experiences of patients undergoing cingulotomy for pain with those having a similar procedure for OCD. Both report that the awareness of pain or obsessional anxiety continues to be present but that it somehow does not bother them as much and that it is easier to divert the obsessional thought or pain into the periphery of their attention. Interestingly, obsessional patients who respond to SRIs also often report they do not seem to feel as strong an urge to complete the compulsion and that the obsessional cue

does not carry the affective weight that it did prior to treatment. Similarly, patients treated with SRIs or surgery often notice they are much less likely to cry or feel strong negative or positive emotions. It is also worth noting the parallel between the mild euphoria and lack of social concern seen after prefrontal procedures with the acute hypomanic/manic response to high amplitude stimulation of the vALIC or STN. This is seen only rarely following cingulotomy or capsulotomy as is the acute pleasurable feeling reported with high amplitude vALIC DBS.

THE DAWN OF STEREOTACTIC NEUROSURGERY FOR PSYCHIATRIC DISORDERS

As the adverse effects associated with frontal lobotomy and leucotomy came into sharper focus in the late 1940s, neurosurgeons and their neuropsychiatric collaborators turned to test the efficacy and safety of more limited procedures that interrupted the connections between the frontal lobe and thalamus. This was made possible by the development of the first stereotaxic frame for use in humans by Spiegel and Wycis [63]. While most of these procedures targeted frontal white matter tracts, Spiegel and Wycis [64] and Hassler [65] targeted the mediodorsal and intralaminar thalamic nuclei themselves. Postoperatively both investigators noted recent memory loss and psychomotor akinesia. There was also an increase in weight and appetite, but it was reported that most of the long-term undesirable personality changes associated with prefrontal lobotomies such as distractibility, childishness, and lack of social tact were not present. They reported there was no change in IQ, though it was noted that "patients treated serious issues with inappropriate humor" and that they were mildly euphoric. At 2 years follow-up, Hassler noted psychomotor akinesia and recent memory problems after DM thalamic and intralaminar thalamic lesions. Due to the significant vascularity of these thalamic nuclei, devastating hemorrhages occurred in 10% of the sample, dampening further enthusiasm for direct thalamic lesions.

While advocating for lesioning white matter tracts between the prefrontal cortex and its subcortical connections, Rylander [66] and Grantham [60] opposed section of fibers from the lateral portion of the cortex as they felt it resulted in adverse personality changes without contributing significantly to the therapeutic outcome…"*the medial portion of the cortex with its orbitotemporal insulocingulate complex and connection with the dorsomedial thalamus are the basis of affect and emotion. Ventromedial quadrant coagulation appeared to cause loss of sexual and moral inhibition inertia and mild euphoria.*" In 1948, Scoville described his method of cortical undercutting which proposed three different cuts, the convex side of the frontal lobes isolating areas 9 and 10, the whole orbital surface, and the medial side comprising areas 24 and 32 [67]. The following year, the work of Columbia Greystone Associates was published with ablation of different areas of the orbital and medial cortex in 24 chronic schizophrenic patients [68]. The authors embarked on their new surgical approach in an effort to discover whether small and specific ablations of well-circumscribed areas of the frontal cortex might have the same beneficial effects that leukotomy (the standard form of prefrontal lobotomy) does, without the undesirable but unavoidable side effects of the extensive standard operation. They also wished to discover which areas would have to be ablated to achieve these results. Prior to this work, it was an open question whether the extent of the operation per se had anything to do with its effects or whether interference with certain specific cortical systems was responsible for the desirable results. If the latter were the case, they hypothesized that it should be possible to minimize the undesirable side effects by narrowing the area operated on. Decreases of anxiety appeared to be connected with ablation of areas 9 and 10. Cairns and LeBeau [69] reported good results and few side effects after removal of the anterior part of the cingulum

in anxiety states and obsessional neuroses. Undesirable personality changes were reported to be very slight with orbital undercutting or cingulotomy. In the mid-1950s, surgical approaches faded away with increasing evidence of the long-term adverse effects of lobotomy and the introduction of psychotropic drugs. In a study that predates the emergence of DBS and recording, Peterson et al. [70] studied the electrical potentials in the frontal lobes of 73 patients with 2500 implanted electrodes. In the plane of the coronal suture, delta waves of 2–4 cps were "invariably" recorded from an area 1–2 comes in diameter from the ventral medial quadrant of the frontal lobe, leading to selective ablations in that area in 63 patients, most of whom were schizophrenic. Only sixteen patients improved enough to be released from the hospital.

These early results led investigators to target the major white matter tracts that connect the medial and orbital frontal cortex with other cortical and subcortical structures including: (a) the cingulate bundle(cingulotomy) (b) the anterior limb of the internal capsule (ALIC) (anterior capsulotomy) and (c) and the sub caudate white matter and the uncinate fasciculus (sub caudate tractotomy and limbic leucotomy). It is striking that most of the studies completed between 1950 and 1990 demonstrated efficacy in 50–70% of severely ill OCD patients while reporting minimal adverse effects. We will give a brief overview of the three procedures that have been primarily used in the treatment of intractable OCD, cingulotomy. anterior capsulotomy and limbic leucotomy, focusing on adverse and positive effects in frontal lobe function. It is worth noting that in spite of improvements in targeting, diagnosis, and the use of standardized outcome measures, most of these studies focused primarily on safety and efficacy and failed to record many of the rich clinical observations that characterized early studies of prefrontal leucotomy.

CINGULOTOMY 1950–1990

Ballantine reported on a series of 198 patients with intractable OCD, anxiety, depression, and pain who underwent anterior cingulotomy with a mean follow-up of 8.6 years [71]. Bilateral lesions were placed in the cingulate bundle 6 mm from the midline and from 0 to 4 cm posterior to the anterior tip of the lateral ventricle. Lesions were 1 cm in diameter by 2 cm long. Patients with anxious depression had the best outcome, with OCD and schizophrenia improving less predictably. Twenty-five percent of the OCD patients were rated as being functionally well, 31% as improved, and 41% with slight or no improvement. There was no evidence of lasting neurologic or behavioral deficits reported; and there was a significant gain in verbal and nonverbal IQ post operatively. The only decreased score in neuropsychological testing was in the Taylor complex figures test in patients over 40 at the time of operation. This performance deficit correlated with the number of previous ECT treatments the patients had undergone.

An independent group of psychologists at MIT, experts at neuropsychological function and brain trauma, were enlisted by the US Congress to study cingulotomy patients as part of a white paper on psychosurgery in 1975 [52, 72]. They followed 18 of these patients prospectively with a series of in-depth interviews of the patients and their families, as well as an intensive battery of 24 neuropsychological tests administered preoperatively, before 4 months, as well as 4 months to 10 years after surgery. In summarizing their findings the investigators note *"Repeated analysis of the life history data and interview material has so far failed to disclose any obvious costs of the intervention. The patients as a group show a slight gain in employment and all patients and relatives insisted that they were capable of an appropriate depth of feeling…..looking at the total pattern of results it may be said that there were no lasting effects of the cingulotomy per se on the 24 behavioral tasks though there were significant effects associated*

with age and the number of ECT sessions. The Wisconsin card sort at the less than four-month follow-up point showed that 4 of 12 patients scored lower, 2 of 12 the same, and 6 of 12 improved. Two of the four that showed a deficit that could be followed up at a later time point had reverted to their preoperative level of performance. For other presumed indicators of frontal lobe function there was no change in verbal fluency, nonverbal fluency, Porteus maze and delayed alteration tasks." They conclude by stating "*In sum, contrary to our expectations when this survey was begun, the cingulotomy procedure by itself did not visibly impair the patients capacity to perform a wide range of tasks in the laboratory or in real life….perhaps the difficulty of detecting any specific adverse effects of the cingulate lesions should have been expected since one major outcome of all of our previous studies had been the observation of considerable resiliency of human behavior after small penetrating brain wounds unless they were critically placed.*"

Kelley and Richardson published a series of papers on sub caudate leucotomy which combined a single bilateral lesion in the cingulate bundle with an additional lesion in the lower medial frontal quadrant about 10 mm rostral to the anterior commissure in the region of the ventral half of the ALIC and adjacent ventral caudate [73–75]. Confusion, extreme laziness, and stereotyped perseverative behavior were present in the immediate postoperative period but cleared within a few weeks. Mild lethargy or laziness was seen in 8 of 66 patients at 16-month follow-up. Obsessional neurotics showed an 89% improvement at follow-up with no change in intelligence.

ANTERIOR CAPSULOTOMY 1960–1990

Talairach [76] was the first to lesion the ALIC, with the surgical procedure being further refined for OCD patients by Herner and Leksell [77]. Thermal electrodes were introduced along with the capsule in the coronal plane approximately 17 mm in front of the anterior commissure and a lesion was made that extended 20 mm from the dorsal to the ventral extent of the capsule that was 8 mm wide in the coronal plane. The lesion severed corticofugal fibers to and from the medial, orbital, and dorsolateral aspects of the prefrontal cortex and their subcortical targets including the striatum, thalamus, hypothalamus, and brainstem. Intraoperatively, it was noted that when the last lesion was produced, the patient became confused and disoriented for 24 h. Bingley et al. reported on a follow-up study of 35 OCD patients post capsulotomy that was prospectively followed by Rylander [78]. Sixty to seventy percent of the patients were reported to be significantly improved. Ten days after surgery, EEG changes were present in 90% of the patients consisting of bilaterally synchronous bursts of rhythmic slow waves with a maximum in the frontal regions. These EEG changes had normalized in patients at 1-year follow-up [79]. A characteristic feature of the early postoperative period was that patients suffered from psychomotor akinesia for several weeks. Many needed to be encouraged to get out of bed and get dressed. As noted previously, Rylander was among the first to report personality alterations in patients undergoing lobotomy or leucotomy [61]. His observations that the anterior capsulotomy patients did not manifest personality changes seem all the more telling, as he knew what subtle signs to look for from previous experience with patients who had undergone prefrontal leucotomy. Using both patients as well as relative interviews and neuropsychological testing, he found that intellectual function was either stable or improved when comparing pre to post capsulotomy performance. Tests of memory, concentration, abstract thinking, personality, and general intelligence were either stable or improved. He pointed to an improvement in overall anxiety, obsessive thinking, and mood as well as decreases in neuroticism, shyness, and sensitivity to criticism. These data conflicted with those of Kullberg who reported that several capsulotomy patients in their sample suffered from emotional blunting, diminution of inhibition, elevation in mood, and loss of goal-directed behavior [80].

CINGULOTOMY 1990–2020

In a series of follow-up papers [19, 20, 81, 82] the group at MGH reported on the prospective long-term follow-up of 64 patients who had anterior cingulotomy for intractable OCD between 1989 to 2009 (mean follow-up of 64 months). Thirty-six patients had a single pair of lesions and twenty-eight had a triple pair of lesions located along the cingulate bundle stretching from the genu of the corpus callosum posteriorly. There was no significant difference in outcome between the single and triple paired lesions. Thirty-five percent of patients had a greater than 35% drop in the YBOCS with an additional 7% having a 25% drop. Patients who failed to respond had a second procedure either extending the cingulate lesion or adding a subcaudate tractotomy. Five patients had temporary postoperative memory difficulty that resolved days to months later. Four patients had noticeable postoperative abulia, 1 after the initial cingulotomy and three others after the addition of a sub caudate tractotomy to the cingulotomy. The abulia resolved in the 12 months following the procedure.

Jung et al. reported on the 1- and 2-year follow-up of seventeen patients who had anterior cingulotomy for OCD [21]. Forty-seven percent of the patients experienced a greater than 35% drop in the YBOCS at follow-up. Lesions were placed slightly more anterior in the cingulate bundle than in the MGH cohort. In addition to reporting adverse events, patients completed an extensive battery of neuropsychological tests including several measures of frontal lobe function including the Rey Complex Figure Test, the Wisconsin Card Sort Test, the controlled Oral Word Association Test, and the Hopkins Verbal Learning Test. The results showed no significant preoperative versus postoperative declines in any of these measures and there was a significant improvement in the WCST scores. Three patients complained of recent memory problems but these resolved within three months after surgery.

Cohen et al. [83–86] studied 12 pts who had a single bilateral cingulate lesion and who were followed up at 3 months and 12 months post-surgery. Immediately after cingulotomy, mutism, akinesis, blunted effect, lethargy, and apathy were common. These severe symptoms resolved rapidly, and 3 months after surgery most patients had returned to baseline across most cognitive domains including language, visual, motor, memory, and intellectual functioning. Despite this recovery, many families reported that subtle personality and functional changes remained, particularly continued behavioral passivity. Deficits of executive control and attention also persisted, with spontaneous response production most affected (Spontaneous Utterances, Object Construction, Design Fluency), a pattern of impairment commonly observed among patients with frontal lobe damage. At 12 month follow-up, most executive and attentional impairments were resolved, and residual impairments were more circumscribed. Yet impairments of intention and spontaneous response production remained, along with mild deficits of focused (Stroop) and sustained (ARCPT) attention. Patients continued to show performance variability, slowed processing, and vulnerability to interference. Although relatively mild, these deficits are noteworthy, given that other cognitive domains and attentional functions were unaffected. Cingulotomy did not affect performance on tasks that placed primary demands on sensory selective attention (e.g., Letter Cancellation), attention span, and working memory (e.g., Digit Span). Learning and memory were also intact.

Banks et al. [87] reported on fourteen OCD patients who had cingulotomy as well as high resolution structural and diffusion imaging scans. They identified a gray matter cluster just anterior to the lesion in the right anterior cingulate that correlated with the poor response using voxel-based morphometry. Using diffusion

connectivity measures, they also found increased right-sided connectivity between the lesion site and the caudate that predicted enhanced treatment response.

McGovern et al. [88] conducted a comprehensive review of the literature which included 85 studies examining the role of the dACC in OCD. The majority of the studies (72 of 85) consisted of imaging studies. Thirteen of 23 studies identified increased metabolic activity at rest in OCD compared to controls. Electrophysiological measures of error-related negativity have in general found an enhancement in OCD while task-based imaging has produced conflicting results. The evidence underlying the role of ACC in symptom provocation was deemed equivocal with too few studies to make concrete conclusions. Ten of 20 studies have shown reduced gray matter volume in dACC in OCD vs controls. The authors note that very few prospective studies of pre-post cingulotomy or capsulotomy have tested frontal lobe behavioral tasks, task-based imaging of those tasks, or resting-state imaging.

Summarizing the large body of literature on the functional role of the anterior/dorsal cingulate is beyond the scope of the current paper. The reader is referred to two additional excellent reviews on the subject [89, 90]. Intraoperative single or multiunit recording or stimulation prior to making a lesion offers a unique opportunity to extend findings of electrophysiologic studies of the prefrontal cortex in primates to humans. While most of these studies have been conducted in the context of DBS trials, several electrophysiologic and behavioral studies have been published about cingulate function in humans in OCD patients undergoing cingulotomy. The small number of subjects tested limits the conclusions that can be drawn from these results. They are generally in agreement with electrophysiologic studies done in non- human primates as well as imaging studies in humans. These studies point to the anterior cingulate's key role in action initiation and monitoring and their relationship to salient events in humans.

Ochsner et al. [91] examined pre to post-performance changes in visual attention and cognition in one patient who had undergone anterior cingulotomy. They demonstrated deficits in the ability to sequence novel cognitive operations required to generate multipart images as well as the ability to select a controlled and practiced response versus an automatic one following cingulotomy.

Williams et al. [92] used intraoperative single-unit recordings in five patients undergoing cingulotomy to evaluate the role of the dACC in reward-based decision making. Subjects performed a task where they were instructed to make specific movements in response to changing monetary rewards. In many neurons, activity increased in response to a diminished reward and was also predictive of the movement ultimately made. After dACC ablation, subjects made selectively more errors when they were required to change movement based on reward reduction.

Gentil et al. [93] studied preoperative stimulation at the cingulate and sub caudate target sites and found that stimulation was accompanied by increased autonomic arousal as measured by skin conductance but not heart rate acceleration. Srinivasan et al. [94] studied the immediate effects of anterior cingulate ablation on action initiation in six OCD patients. Three patients had pre and immediate postoperative simple reaction time tests while another three patients completed a pre and post-operative reward-based decision task. The frequency of false starts following a visual cue increased in the simple reaction task.

Sheth et al. [95] demonstrated that the modulation of current dACC activity by previous activity produces a behavioral adaptation that accelerates reactions to cues of similar difficulty to previous ones, and retards reactions to cues of different difficulty. Furthermore, this conflict adaptation was abolished after surgically targeted ablation of the dACC. They concluded that the dACC provides a continuously updated prediction of expected cognitive demand to optimize future behavioral responses. In situations with stable cognitive demands, this signal promotes efficiency by

hastening responses, but in situations with changing demands, it engenders accuracy by delaying responses. Sklar et al. [96] tested nine OCD patients undergoing cingulotomy, identifying a population of rostral ACC(rACC) neurons that respond differentially or in a graded manner to cognitively demanding high- and low-conflict Stroop tasks, including those with emotional valence [97]. These data suggested that rACC neurons may be acting as salience detectors when faced with conflict and difficult or emotional stimuli, consistent with neuroimaging results of rACC responses to abrupt sensory, novel, task-relevant, or painful stimuli.

ANTERIOR CAPSULOTOMY 1980-PRESENT

Mindus and Myerson reported on the outcome of two capsulotomy cohorts: one with severe intractable anxiety and the other with intractable OCD [98]. Patients were either lesioned with the standard thermocapsulotomy method or with a non-invasive radiosurgical instrument developed by Leksell called the gamma knife. Twenty-four patients with intractable anxiety were followed at 3, 6, 9, and 12 months following the procedure as well as a long-term follow-up of a mean of 8 years. Nyman and Mindus administered an extensive neuropsychological battery to seventeen of these patients [99, 100]. Tests showed either an improvement or a stable pattern following capsulotomy with the only exception being the Wisconsin card sort which showed an increased number of perseverative errors in five of the seventeen patients. In a separate study, Mindus et al. gave the Karolinska Scale of Personality to 24 patients at baseline and 1-year following thermocapsulotomy [22]. At 1-year follow-up significant decreases (towards normality were seen in eight of the scales). Scales related to impulsiveness hostility and aggressiveness were within the normal range. Ruck et al. reported on an independent long-term follow-up (mean of 13.5 years) of 26 bilateral thermocapsulotomy patients with severe anxiety who had no OCD [101]. In this study, 7 of 17 patients were rated as having significant adverse effects with the major symptoms being apathy and dysexecutive behavior. The authors were not aware of rating instruments for symptoms of frontal lobe function at the time of the study, so they made a simple scale that measured executive function, apathy, and disinhibition. One of the patients was rated as severe in all three measures, two moderate in executive function and apathy and one severe in executive function and apathy. Only three out of 26 had scores greater than three and two of those three had been reoperated on due to continued symptoms. These patients also made more perseverative errors on the Wisconsin Card Sort Test. The authors concluded that although many patients benefited from the procedure that a minority was left with significant long-term adverse cognitive effects.

In a separate long-term follow-up (mean of 10.9 years) of the OCD cohort, Ruck studied 25 patients with intractable OCD that had anterior capsulotomy using either thermocapsulotomy or the gamma knife [23]. Twelve out of 25 patients sustained a greater than 35% drop in the Yale Brown Obsessive Compulsive Scale (Y-BOCS). Significantly, none of the patients was working at follow-up. Two patients suffered from severe executive dysfunction, apathy, and disinhibition while six had at least moderate impairment on one of these domains. The authors concluded that the procedure was clearly efficacious in reducing symptoms but that some patients were left with significant cognitive impairment.

In an effort to minimize adverse effects, Rasmussen et al. [102] began doing ventral gamma capsulotomies (gvALIC) that were located 8–10 mm anterior to the posterior border of the anterior commissure in the coronal plane and that targeted fibers connecting the orbital and medial frontal cortices with the thalamus and brainstem, leaving the dorsolateral cortical fibers

that ran in the dorsal portion of the capsule intact. At 3-year follow-up they found that thirty-one of fifty-five patients (56%) had an improvement in the primary efficacy measure, the (YBOCS), of greater than or equal to 35%. Standard neuropsychological testing found that patients' performance on each of these tests improved at follow-up. Four patients exhibited increased post-operative apathy that dissipated during the year following the procedure. In addition, three patients experienced the development of cysts around the target site at 5 years follow-up, two of which were asymptomatic and a third that was associated with radionecrosis that ultimately led to a vegetative state. The majority of patients returned to work and or school: and at 20 years follow-up are leading productive lives as physicians, judges, writers, engineers, and other professions that require intact executive function. Two additional recent reports of OCD patients with thermal capsulotomies from Eastern Europe have documented capsulotomies efficacy and safety with no Impairment seen in frontal function [103, 104].

Kim et al. [105] were the first to report on the use of high-intensity focused ultrasound to make ventral capsulotomy lesions in 11 OCD patients. At 12 months, 6 (54.5%) patients were responders and 3 (27.3%) patients were partial responders. At 24 months, 6 patients were responders, 2 (18.1%) were partial responders and 1 had achieved full remission. The mean Memory Quotient score improved significantly across the 24- month follow-up period (F3, $6.5 = 236.3$, $p < 0.001$). They observed no significant changes in K-WAIS, COWAT, Stroop, or Digit Span scores. There were no adverse cognitive effects noted at 6 and 12-month follow-up with improvement in the Memory Quotient Scale and no change in frontal measures. Davidson et al. [106] created a single 7 mm lesion using high-intensity focused ultrasound to study the cognitive effects of a single lesion in the anterior capsule in ten patients with refractory OCD or depression. They followed patients prospectively at 6 and 12 months utilizing tests of executive function, memory, and processing speed. At a group level, scores were stable or mildly improved at both 6 and 12 months.

Patients endorsed fewer symptoms of apathy at 6 and 12 months and fewer overall frontal symptoms at 12 months.

Paiva et al. [107] conducted a personality assessment using the Revised NEO Personality Inventory (NEO PI-R) and Cloninger's Temperament and Character Inventory (TCI) in 14 intractable OCD patients before and 1-year after GVC. Overall, no deleterious effect was found in personality after GVC. Responders had a reduction in neuroticism ($p = 0.043$) and an increase in extraversion ($p = 0.043$).

Zhang et al. [108] administered the Iowa gambling task to 24 OCD patients preoperatively and 3–5 months following bilateral anterior capsulotomy. Twelve of these patients had a long-term follow-up at a mean of 3 years after surgery. There were no significant differences in decision-making between the preoperative and 3–5 month follow-up groups. The decision-making ability of the long-term follow-up patients had improved to the level of healthy controls at long-term follow-up.

NEUROSURGICAL APPROACHES TO OCD AND THE FRONTAL LOBES: DBS
In contrast to ablative procedures, DBS has the advantage of being reversible (expandable) and adjustable [109, 110]. In 1999, DBS targeting the ALIC was found beneficial in three of four cases of intractable OCD [111]. Since then, DBS of the ALIC [112] or neighboring targets (i.e., the VS or nucleus accumbens (NAc), a subregion of the VS) have shown response rates in the range of 40–70% [109, 113–117]. In 2010, the FDA approved a humanitarian device exemption (HDE) for vALIC DBS in intractable OCD based upon the device's safety and its probable benefit for up to 8000 people a year in the US that would meet criteria for implantation.

The exact "target" for the DBS electrode has been a matter of debate. Some studies have focused on deep gray matter structures such as the VS/NAc or bed nucleus of the stria terminalis (BNST) [118] as critical mediators of response. Others have suggested that these nuclei are useful guideposts, but that the white matter fibers connecting PFC and thalamus that course through the vALIC superjacent to these nuclei are critical, as they convey the influence of neuromodulation to the wider symptomatic network [119–121]. The fact that DBS targeting similar white matter pathways in disparate brain regions (e.g., VC/VS and STN) achieves comparable results [122] provides support for the white matter hypothesis. Li et al. analyzed data from four cohorts of patients ($N = 50$) who underwent DBS targeting at either the ALIC, NAc, or STN and identified a specific white fiber tract that was associated with optimal clinical outcome [120]. This bundle connects frontal regions directly to the STN and may represent a unified connectomic target for successful clinical response to DBS in OCD. However, as noted by Robbins et al. [123] while DBS in the vALIC led to improved mood, DBS in the STN site significantly improved cognitive flexibility. Robbins et al. [123] went on to conclude that the two sites appear to improve symptoms in distinct symptoms mediated by different circuits,

The original hypothesis that high-frequency DBS (e.g., 130 Hz) would act as "functional ablation" has been challenged by emerging basic neuroscience research showing that the therapeutic mechanisms of DBS are far more complex [124, 125]. In a study of NAc DBS in OCD, repeated resting-state fMRI scans showed that DBS normalized (increased) NAcc activity and reduced excessive connectivity between NAcc and the prefrontal cortex [126].

While VS DBS is an important option for intractable OCD, there is much room for improvement in outcome rates, the magnitude of response, and mitigation of DBS-induced side effects [109]. Even among DBS "responders," as defined by a 35% reduction in symptom severity on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) few achieve remission, the response of OC symptoms is delayed (typically no earlier than a month), and maximal benefit is not achieved until 6 months or later [113].

Programming adjustments are made largely on the basis of acute beneficial effects on "anxiety", "mood" and "energy" as described by the patient and observed by the clinician. In contrast to DBS for tremor, immediate effects on the core symptoms of OCD (i.e., obsessions and compulsions) are not discernable in the acute programming session. Instead, parameters are adjusted, in a trial-and-error fashion, based on changes in OCD symptom severity since the last visit as reported by the patient or informant. Importantly, VS DBS-induced elevated mood is also used as a surrogate marker for OCD as some studies suggest it may be a positive predictor of eventual OCD outcome [109, 117, 127–129].

Sustained positive effects of DBS on mood invariably precede any clinically apparent improvement in OCD [113]. On the other hand, improvement in mood does not guarantee a successful outcome for OCD. Clinician- and patient-rated measures of increased energy (e.g., higher "vitality" and lower "fatigue" on the profile of mood states (POMS)) accompany positive mood effects of VS DBS in OCD [113].

Apart from its possible predictive value [130, 131], DBS-induced mirth also represents a potential risk: the development of hypomania or mania [127, 131]. Despite the programmer's best efforts to titrate the dose of stimulation, some patients go on to exhibit a behavioral syndrome marked by elevated mood, increased energy, pressured speech, decreased need for sleep, and sometimes impulsivity [127, 132] These signs and symptoms are reversible with adjustments in DBS settings. However, turning down the amplitude or reducing the pulse width may lead to a loss of clinical benefit. Striking the right balance between negative and positive valence mood states is often challenging. The risk of developing DBS- induced hypomania is unrelated to a history of

bipolar disorder [131]. De Haan et al. [133, 134] have made a careful qualitative assessment of the long-term effects of vALIC DBS on the lived experience and personality of 18 patients with intractable OCD. Many of their observations are eerily reminiscent of earlier lesion studies with some patients reporting less concern about the social consequences of self-motivated behaviors and even changes in interest in music and reading. For the most part patients and their significant others describe these changes as beneficial and allowing them to grow into their "true selves." Continued qualitative observation of these patients, in combination with more defined task-based approaches to changes in frontal lobe function, are needed to understand how DBS and lesions affect both symptoms as well as an understanding of self.

A DBS system that could detect and correctly classify a key component of OC behavior based on brain recordings would represent a leap forward in biomarker development for psychiatric disorders. Accomplishing the next step of automatically adjusting VS stimulation in response to the changing needs of the patient would have tremendous potential for advancing therapy over the fixed-dose approach only available today. The potential benefits to patients would be automatic adjustments of DBS stimulation in the ambulatory environment to better control fluctuating OC symptoms as well as mitigation of behavioral side effects of DBS. NIH-funded studies are underway using next-generation DBS devices that can record local field potentials (LFPs) as well as deliver neurostimulation (NCT03457675, NCT03244852) [135].

The feasibility of recording LFPs in OCD patients chronically implanted with a DBS device that can both stimulate and sense was recently demonstrated [136]. These types of studies may yield insights into the neural signatures of behavioral states associated with changes in OCD symptom severity [135]. The ability to record neural data from patients in their natural environment, time-locked with behavior and physiology, offers a unique research opportunity to test hypotheses about the neurocircuitry of OCD.

DISCUSSION

After thoroughly reviewing the history of lesion studies for intractable OCD, one cannot help but take note of the minimal loss of function given the size and extent of the lesions. The consistent outcome of reduced symptoms and improved function in the most intractable OCD patients across multiple investigators and over a 70 years timeline with few adverse events is even more striking. While it is certainly true that the number of patients who have undergone preoperative and postoperative testing using recently developed cognitive measures of prefrontal cortical function is few, those studies that do exist suggest an alternative explanation, i.e., the highly distributed parallel processing that characterizes prefrontal brain networks and the resulting remarkable resilience of the human brain to injury. This hodologic model of frontal function that emphasizes the redundancy of cortical function and the importance of white matter cortical-subcortical connections has been validated with electrical stimulation studies of patients undergoing frontal resections for low-grade gliomas [137].

Studies of motor intent using brain-computer interfaces have demonstrated that output from multiple cortical areas outside of the premotor cortex can be used to generate algorithms of intent for action. Similarly, there can be no doubt that the detection of salience, the representation of value, hierarchical action selection, and the monitoring of action-outcome that form the basis of goal-directed behavior are made up of highly distributed interacting networks that rely on parallel processing. Additional studies of the effect of DBS and lesions on frontal lobe tasks, pioneered by Robbins group at Cambridge, demonstrating abnormal frontal lobe function in non-surgical OCD patients, are needed [123, 138]. The delayed onset of efficacy following lesioning is poorly understood but it seems likely that major alterations in network dynamics are taking place. The fact that following traditional thermocapsulotomy and cingulotomy confusion and motivation are present initially but fades over weeks to months is evidence of this dynamic process. A more detailed delineation of the time course of those dynamics is needed. For a long time, neurocognitive and behavioral functions have been considered in associationist terms of areas and tracts, the global principle being that data were processed in localized cortical sites with the serial passage of information between zones through white matter fibers. In the connectomal account, neural functions are conceived as resulting from parallel delocalized processes achieved by distributed subgroups of connected neurons rather than discrete epicenters.

MacLean concluded from an evolutionary perspective that human neuropsychiatric conditions are likely to have their origin in the connections of the prefrontal cortex and the rest of the brain since the prefrontal cortex had not been subject to the pressures of natural selection that phylogenetically older parts of the brain had been. Elsewhere in this issue, Amhari and Rauch have summarized the wealth of data that has begun to accumulate that implicates frontostriatal thalamic connections in the pathogenesis of OCD.

The history of neurosurgical approaches to the treatment of intractable psychiatric disorders has been to make increasingly smaller lesions that minimize adverse outcomes while maintaining efficacy. As a field, we have moved from frontal lobotomy to bimedial leucotomy to thermocapsulotomy and cingulotomy to ventral capsulotomy. Even prior to 1950, investigators were moving away from the dorsolateral part of the cortex to its medial and orbital surfaces where value and emotion seemed more likely to emanate from. The neuroimaging studies reviewed in this issue led Rasmussen et al. [104] to target the ventral half of the capsule that contain corticofugal fibers from the medial and orbital surfaces as well as the frontal pole as opposed to the dorsal half of the capsule that contains corticofugal fibers emanating from the dorsolateral cortex. The efficacy of single bilateral lesions in the ventral most quarter of the ALIC that contain primarily orbitofrontal and ventromedial fibers and a single lesion of the capsule just dorsal to the ventral lesion that appears to contain VLPFC and cingulate as well as frontal pole fibers have failed to demonstrate the same degree of efficacy as the larger ventral lesion [104, 139]. While some investigators continue to search for the magic spot that could help define the pathophysiology of the disorder and the mechanism of the therapeutic response, others suggest that we are lesioning a highly distributed system and that a certain percentage of that distributed network needs to be lesioned to achieve an optimal outcome.

Recently, progress has been made in trying to more precisely define the anatomy of exactly where these fibers run in the capsule in macaques by combining high-resolution diffusion tensor imaging(DTI) with anterograde and retrograde tracers in the same animal and then using this to interpret high-resolution DTI in humans [121, 140–142]. High-resolution DTI in humans with proven validity and reliability would be a major step forward in advancing our understanding of how to design individualized lesions. It would be important to know a detailed map of which efferents and afferents are being affected by the cingulotomy and capsulotomy lesions and how these might differ across individuals, given the same lesion.

Finally, follow-up interviews with patients undergoing capsulotomies and their relatives have revealed similarities in what they say changes that lead to a positive therapeutic outcome [102]. They all report a lessening of the anxiety associated with a cue or context that brings on the obsession, a reduction of anxiety in anticipation of such an encounter, and a reduction in the urge to do a compulsion. The consequence of the obsession does not seem to have the same weight; they do not feel so responsible for harm coming to others. They report living more in the present as opposed to the future. Interestingly, one hears similar comments from patients who have had a good outcome from the SRIs.

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AUTHOR CONTRIBUTIONS

SAR and WKG conceptualized the review and wrote the manuscript. Both authors approved the final manuscript.

ADDITIONAL INFORMATION

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