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Neuroimaging and neurocircuitry models pertaining to the neurosurgical treatment of psychiatric disorders

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Contemporary neuroimaging methods have been influential in advancing neurobiologic models of psychiatric disorders. Providing means for measuring indices of human brain structure and function in vivo, these tools enable investigators to test hypotheses about pathophysiology, the changes associated with treatment, and predictors of treatment response [1]. In general, it is anticipated that neuroimaging research will substantially contribute to the ultimate achievement of a pathophysiology-based diagnostic scheme in psychiatry and also help to elucidate the mechanisms of action by which treatments have their effects. Moreover, as the neuroscience of psychiatry evolves, it should be possible to rationally develop new and superior treatments as well as to predict treatment outcomes in a manner that could optimally guide selection among alternative treatments for individual patients in the clinical setting.

As reviewed in this issue, a variety of neurosurgical treatments have been developed in an effort to help people suffering from severe and otherwise treatment-refractory psychiatric disorders—principally obsessive-compulsive disorder (OCD) or major depression (MD). To date, clinical reports suggest that the effectiveness of contemporary neurosurgical treatment for these indications is only modest, whereas the potential for adverse effects is still considerable. Thus, it would be of great value to find ways to improve outcome. One goal is to refine neurosurgical treatments for OCD and MD so that they are safer and more effective; another goal is to identify selection criteria, based on predictors of response, that would enable patients who are unlikely to have good outcomes forego the risks and costs of neurosurgical treatment.

In fact, despite a resurgence of interest and accelerated research in this field, little is known regarding the mechanisms by which neurosurgical treatments for OCD and MD have their beneficial effects. Given recent advances in neuroimaging and neurocircuitry models of these disorders, however, the time seems ripe for a fruitful synthesis of psychiatric neuroimaging and neurosurgical data. I would propose that there is great opportunity for synergy at this interface: neuroimaging and neurocircuitry models of disease can help to guide practical progress in the domain of neurosurgical treatment, and, reciprocally, data from neurosurgical treatment research can provide feedback to inform evolving models of psychiatric disease.

Toward that end, in the current article, I describe neurocircuitry models of OCD and MD, focusing on relevant neuroimaging data. I then review the neuroanatomy of psychiatric neurosurgical procedures and related neuroimaging findings. Finally, I present anticipated future directions of research in this field. This article necessarily extends previous reviews that I have written, together with my colleagues, on related topics [2–6].

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Neuroimaging and neurocircuitry models of obsessive compulsive disorder

Neurocircuitry model of obsessive-compulsive disorder and related disorders

Contemporary neurobiologic models of OCD and related disorders have focused on cortico-striato-thalamo-cortical (CSTC) circuitry. In fact, the influential reviews by Alexander and colleagues [7,8] describing segregated parallel CSTC circuits provided an important framework for subsequent theories of pathophysiology in OCD. Specifically, it has been proposed that the CSTC circuits involving orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and the caudate nucleus are central to the pathophysiology of OCD [6,9]. Further, there is a convergence of evidence to suggest that some primary pathologic process within the striatum might underlie the CSTC dysfunction in OCD. The prevailing theory suggests that a relative imbalance favoring the direct versus indirect pathways within this circuitry lead to overactivity (ie, amplification) within OFC and ACC, the caudate nucleus, and the thalamus resonant with failed striato-thalamic inhibition (ie, filtration) within this same circuitry.

This basic scheme has been extended to provide a comprehensive model for a group of purportedly related disorders called "obsessive compulsive spectrum disorders," encompassing Tourette syndrome (TS), trichotillomania, and body dysmorphic disorder as well as OCD. The "striatal topography model" of OC spectrum disorders suggests that these diseases share the attribute of CSTC dysfunction due to primary striatal pathology and that the clinical picture in each case reflects the topography of pathology within the striatum and hence the constellation of dysfunction across CSTC circuits [6,10]. To elaborate, the notion is that OCD and body dysmorphic disorder, the OC spectrum disorders characterized by intrusive cognitive and visuospatial symptoms, involve caudate pathology, whereas TS and trichotillomania, principally characterized by intrusive sensorimotor symptoms, involve pathology within the putamen and dysfunction of sensorimotor CSTC circuitry.

Most recently, pioneering neuroanatomic research by Haber and colleagues [11] has provided a scheme for considering CSTC function that emphasizes a cascading spiral interaction, rather than segregation, across CSTC circuits. This model of normal CSTC function suggests a flow of information from motivation to cognition to motor behavior. This raises the possibility that OCD (as well as other OC spectrum disorders) might not reflect dysfunction within a single segregated CSTC circuit but rather represent a failure in the smooth cascade of information across the various CSTC circuits. For instance, in the case of OCD, cognitions and motivations to act seem to persist (as obsessions with attendant anxiety, respectively) such that motor output fails to reset these thoughts and motivations, hence driving stereotyped motor repetition (compulsions).

It is evident that neurobiologic models of OCD and related disorders have evolved in parallel with our understanding of the relevant basic neuroscience as well as with accrual of data from patient studies. In this regard, it is useful to review the findings of pertinent psychiatric neuroimaging research.

Neuroimaging studies of obsessive-compulsive disorder

There is now an impressive array of different neuroimaging techniques that can be used in a complementary fashion to advance psychiatric neuroscience. Here, I systematically review how these various methods have been employed to develop a cohesive neurobiologic model of OCD.

Morphometric MRI studies have been performed to test hypotheses regarding regional brain volumes in OCD. In adults with OCD versus healthy comparison subjects, findings of subtle volumetric abnormalities involving the striatum have predominated [12–14]. Moreover, whereas the caudate has been principally implicated in OCD, consistent with the striatal topography model of OC spectrum disorders, studies of TS [15,16] and trichotillomania [17] have principally implicated the putamen or lenticulate, although an initial study of body dysmorphic disorder has also found a subtle abnormality involving the caudate [18].

Such morphometric methods have only modest sensitivity, and some studies have failed to find striatal abnormalities in OCD [19]. Magnetic resonance spectroscopy (MRS) provides a means for measuring the relative concentration of certain endogenous chemical compounds in vivo. In particular, N-acetyl aspartate (NAA) is an MRS-visible compound thought to serve as a marker for healthy neuronal density. Thus, reduced levels of NAA can be detected as

a possibly more sensitive indication of regional neuronal degeneration or maldevelopment characterized by lower neuronal density or sparse arborization. Interestingly, a series of MRS studies of OCD have found reduced striatal NAA [20,21] but normal NAA levels within the lenticulate [22]. These findings converge well with morphometric MRI results and are also consistent with neuroimmunologic research, which indicates that some cases of OCD and related disorders can occur as a consequence of autoimmune-mediated striatal degeneration [23].

There have been several isolated reports of regional volumetric abnormalities beyond the striatum in OCD. In adults, these have included gross increases in white matter volume [12,24] and reduced volumes of OFC and amygdala [25]; in children, these have included abnormal thalamic and putamen volumes [26,27]. Similarly, a single report of reduced NAA within the ACC in OCD has been published [21].

Functional neuroimaging studies of OCD have likewise produced convergent results implicating OFC, ACC, and the caudate. Neutral state (including nominal resting state) studies have been performed to test hypotheses regarding baseline differences in regional brain activity between patients with OCD and healthy comparison subjects. Across numerous such studies, the most consistent findings in OCD have been relative hyperactivity of OFC, ACC, and, to a lesser extent, the caudate nucleus [28–30].

Symptom provocation methods have been used in conjunction with functional imaging to test hypotheses regarding the brain regions that exhibit changes in activity level in association with OCD patients experiencing obsessions and the urge to perform compulsions. Again, several studies have yielded convergent findings that most consistently indicate increases in activity within OFC, ACC, and the caudate nucleus during the OCD symptomatic state versus a control state [31–34]. Given that such studies are confounded by nonspecific anxiety, it has been instructive to contrast the brain activity pattern associated with OCD symptoms with the patterns reported for other anxiety disorders. In this context, symptom provocation studies of other anxiety disorders, such as posttraumatic stress disorder and specific phobias [35,36], have frequently found activation of ACC and other anterior paralimbic regions, whereas the recruitment of the caudate nucleus and anterolateral OFC seems to be somewhat more specific to the symptomatic state in OCD. Moreover, pharmacologic induction of anxiety attacks in healthy subjects has likewise been associated with increased activity within anterior paralimbic regions but not in anterolateral OFC or the caudate nucleus [37].

Pre- and posttreatment neuroimaging studies are conducted to test hypotheses regarding changes in brain activity profiles associated with successful reduction in symptoms. Several such studies have been performed to investigate the neural correlates of OCD symptom reduction after treatment with serotonergic reuptake inhibitors as well as behavior therapies. A series of studies have demonstrated a reduction of activity within OFC, ACC, and the caudate nucleus after successful treatment of OCD [38–41]. Further, in one of these studies, an interregional correlation analysis indicated that at the pretreatment time point, there was an abnormal positive correlation between right OFC and the right caudate, which was neutralized after successful treatment [40].

Pretreatment neuroimaging data can also be used to test hypotheses regarding predictors of treatment response. A series of studies of this type in OCD have indicated that pretreatment activity within OFC predicts subsequent treatment response [41–44]. To elaborate, in patients with OCD, higher levels of OFC hyperactivity were associated with poorer subsequent responses to treatment with serotonergic reuptake inhibitors [41–44]. Interestingly, in contrast, higher levels of OFC hyperactivity were associated with better subsequent responses to treatment with behavior therapy [42]. These findings are consistent with the idea that serotonergic reuptake inhibitors might have their antiobsessional effects via their action within OFC [45] and that behavioral therapy may have its beneficial antiobsessional effects via extinction mediated by frontoamygdala interactions [6].

Cognitive activation studies have been performed in conjunction with functional neuroimaging methods to test hypotheses regarding the functional integrity of striato-thalamic circuitry in the context of an implicit sequence learning task. Implicit (ie, nonconscious, automatic) sequence learning is known to be normally mediated by CSTC circuitry, and this function may be right-lateralized to some extent [46–48]. Interestingly, however, when patients with OCD were studied while performing such a task, although they exhibited a capacity to learn the sequence information that was comparable to normal subjects, they failed to recruit the right striatum in a normal

fashion [49,50]. Moreover, OCD subjects showed aberrant bilateral medial temporal activation (not seen in normal subjects during implicit sequence learning) in a manner similar to that evidenced when normal subjects are learning information consciously [49–51]. These findings in OCD have been replicated and seem to indicate that patients with OCD are deficient at recruiting the striatum in the service of thalamic gating [49,50,52]. This may explain why patients with OCD have intrusions of information into consciousness that might otherwise be processed nonconsciously by individuals without OCD.

Taken together, neuroimaging studies of OCD support a cohesive model. There is hyperactivity at rest within the OFC-caudate CSTC circuit, which is exaggerated during symptom provocation and attenuated after successful treatment. A similar profile is present within ACC, although this seems to be a more nonspecific finding across anxiety states. Of clinical relevance, activity within OFC predicts subsequent response to treatment with medication or behavior therapy. Further, MRI and MRS studies suggest striatal pathology, which is consistent with cognitive activation studies that indicate deficits in striatal recruitment and thalamic gating as well as possible compensation via hippocampal activation.

Of note, patients with OCD plus comorbid MD exhibit a profile that differs from that of patients with OCD alone [53]. This is particularly germane to the focus of this review, because most patients with severe treatment-refractory OCD who receive neurosurgical treatment also suffer from comorbid MD. Resting state neuroimaging data suggest that patients with OCD plus MD have lower metabolism within the caudate, thalamus, and hippocampus than patients with OCD alone [53]. Further, functional imaging data from before and after treatment with paroxetine suggest that patients with OCD plus MD exhibit increased activity within the striatum after successful treatment, whereas patients with OCD alone exhibit decreased activity within the striatum after treatment [54].

Neuroimaging and neurocircuitry models of major depression

Neurocircuitry model of major depression

Similar to OCD, neuroimaging-motivated neurobiologic models of MD have also involved CSTC circuitry. In addition to the limbic CSTC circuit, prevailing models of MD have focused on other critical elements of the limbic system, namely, the amygdala and hippocampus as well as the hypothalamic-pituitary-adrenal (HPA) axis [2,55–61]. In general, it is useful to consider the clinical characteristics of MD as they relate to different functional domains, which, in turn, map onto a corresponding functional anatomy [57]. MD episodes (both in unipolar MD and bipolar disorder) are characterized by cognitive, motor, and neuroendocrinologic as well as affective disturbances. At the cortical level, the cognitive and motor deficits of MD may be explained by dysfunction within a "dorsal compartment," including anterior, dorsal and lateral prefrontal cortex; dorsal ACC; and parietal cortex as well as premotor cortex. The affective symptoms of MD may be related to dysfunction within a paralimbic "ventral compartment," including subgenual ACC, OFC, and anterior insular cortex. These dorsal and ventral compartments communicate with their striatal counterparts; the dorsal compartment is linked to the dorsal (cognitive/motor) striatum, and the ventral compartment is linked to the ventral (limbic) striatum. Interestingly, the dorsal and ventral compartments seem to be reciprocally inhibitory [36,62–64]. Thus, in MD, grossly, there appears to be hypoactivity within the dorsal compartment and hyperactivity within the ventral compartment.

Importantly, a triad of areas seem to play a critical role in mediating the balance of activity between the ventral and dorsal compartments both in health and disease. The amygdala is positioned to assess the reward and threat value of external stimuli and has the capacity to drive the balance of activity toward the ventral compartment. The pregenual ACC has the capacity to facilitate the restoration of dynamic equilibrium between the compartments via its inhibitory influence over both dorsal and ventral elements [36,62–64]. Finally, the hippocampus, in addition to its role in cognition, has reciprocal connections with the amygdala and projects to the hypothalamus to influence the HPA axis as well as other functions that are disturbed in depression, such as sleep and appetite. Therefore, it is proposed that amygdala hyperactivity and hippocampal inefficacy may be central to the pathophysiology of MD. Of note, it has been proposed that exposure to stress during early development or chronically could represent a risk factor for the evolution of such a profile [65]. Thus, successful treatment of MD (via any of a number of modalities) may

rely on some combination of deactivation of the ventral compartment, inhibition of the amygdala, stimulation (or protection) of the hippocampus, and/or enhanced efficacy of pregenual ACC.

Neuroimaging studies of major depression

In comparison to OCD, the neuroimaging literature on MD is more abundant and more difficult to interpret parsimoniously. The complexity of this area has been exacerbated by clinical heterogeneity; MD studies have included mixed cohorts as well as more homogeneous cohorts of patients with unipolar MD and bipolar MD as well as MD in the elderly and in the context of primary neurologic disorders. In addition, early disparities in how various neuroanatomic terms were applied contributed to confusion over how apparently discrepant findings could be reconciled. Most recently, careful neuroanatomic studies along with functional neuroimaging studies, including those investigating mood states in normal subjects and studies of changes associated with various antidepressant treatments, have begun to yield a more cohesive picture of MD pathophysiology and its resolution.

Structural neuroimaging studies of MD using morphometric MRI segmentation methods have shown reduced volumes of the hippocampus [60,66–71] and the striatum [72,73]. Of note, findings within the striatum have been less consistent [74,75], and studies that segmented the hippocampus and amygdala conjointly have often been negative [76]. MRI studies have also found reduced volumes in prefrontal cortex [73,77], and cortical parcellation methods have been applied to discover reduced volume in subgenual cortex [56,78] and OFC [79]. These structural imaging findings resonate with postmortem studies of MD, which have revealed glial cell loss in subgenual cortex [80] as well as reduced glia and smaller neurons within OFC [81] and cell atrophy within dorsolateral prefrontal cortex [82].

Neutral state functional imaging studies have demonstrated hyperactivity within OFC and anterior insular cortex during MD episodes [83–87]. Although initial studies of MD indicated reduced activity within subgenual cortex [56,88], subsequent correction for reduced volume in that area has revealed relative hyperactivity [56]. Further, these same areas seem to exhibit elevated activity during induced states of transient sadness [59,89] and reduction of hyperactivity in the context of successful antidepressant treatment [59,86,88,90]. Of note, however, activity within OFC seems to be inversely correlated with MD symptom severity (as well as with anxiety in some cases), suggesting that this region may be recruited in a compensatory fashion [34,55,86].

Elements of the dorsal compartment, including anterior and dorsolateral prefrontal cortex as well as dorsal ACC, have been found to exhibit reduced activity during MD episodes [91]. Likewise, reduction in activity within the dorsal compartment has been observed during transient induction of sad mood [59]. Conversely, hypoactivity in these regions returns toward normal after successful antidepressant treatment of patients with MD [59,92]. Moreover, cognitive activation studies have indicated an attenuated capacity for patients with MD to recruit dorsal ACC successfully [93].

The amygdala has been found to be hyperactive in neutral state studies of patients with MD [86,94], and there is some suggestion that this finding might be left-lateralized [86]. The severity of MD symptoms is correlated with amygdala activity [86]. Although hyperactivity within this region is attenuated with successful treatment, some residual hyperactivity may persist even during extended remission of MD [86]. Functional imaging studies using pictures of human faces displaying various emotional expressions have provided a means for assessing amygdala responsivity to social cues of varying arousal value and valence [95,96]. Further, by presenting such face stimuli beneath the level of conscious awareness, it has been possible to probe automatic aspects of such amygdala responses relatively dissociated from the top-down influences of frontal cortex [97]. Using this approach in conjunction with functional MRI, it has been found that patients with posttraumatic stress disorder exhibit exaggerated responsivity within the right amygdala to threat-related stimuli [98]. Interestingly, a subsequent analogous study of patients with MD revealed exaggerated amygdala responses within the left amygdala; moreover, the exaggerated response in the left amygdala was attenuated toward normal after successful treatment with antidepressant medication [99]. Importantly, recent functional imaging studies of healthy subjects seem to suggest that the right amygdala may be more temporally dynamic in its response, exhibiting prompt habituation effects, whereas the left amygdala seems to exhibit a more temporally stable response that is highly valence dependent

[100]. This provides a framework for understanding lateralized differences in amygdala function across mood and anxiety disorders. To elaborate, the prevailing negative bias that is characteristic of MD could be associated with left amygdala dysfunction, and the exaggerated response and failure to habituate to threat-related stimuli that is characteristic of selected anxiety disorders could be associated with right amygdala dysfunction [101]. This could also help to explain the high comorbidity that is observed across mood and anxiety disorders, given that various etiologies of amygdala dysfunction might be agnostic to the laterality of pathology.

Although studies of MD have repeatedly noted volumetric reductions in the hippocampus, resting state functional neuroimaging studies have rarely found hypoactivity in this region [53,102]. Rather, during the course of a successful trial of antidepressant medication, MD patients seemed to exhibit increased activity within the hippocampus at week 1 and subsequent decreases in hippocampal activity by week 6 [58]. Likewise, although resting state functional imaging studies of MD have not typically indicated baseline abnormalities in pregenual ACC, pretreatment levels of activity within this area have been found to predict subsequent response to antidepressant medication [103]. Specifically, individuals with higher levels of pregenual ACC activity before treatment exhibited a superior antidepressant treatment response.

Anatomy and imaging of neurosurgical treatments for major depression and obsessive-compulsive disorder

As outlined in detail throughout this issue, ablative neurosurgical treatments for OCD and MD include anterior cingulotomy, subcaudate tractotomy, limbic leukotomy, and anterior capsulotomy. In fact, the neuroanatomic ramifications of these ablative procedures remain incompletely understood.

In the case of anterior cingulotomy, the lesions are placed within dorsal ACC and typically impinge on the cingulum bundle [104]. Thus, in addition to reducing cortical mass and activity within dorsal ACC, it is likely that these lesions modify cingulo-striatal projections and disinhibit pregenual ACC. Given the composition of the cingulum bundle, it is also possible that its disruption in cingulotomy could influence reciprocal connections between the ACC and several other structures, including OFC, the amygdala, the hippocampus, or posterior cingulate cortex [105]. In fact, comparisons of presurgical with postsurgical MRI data indicate that volume may be reduced within the caudate nucleus and posterior cingulate cortex by 6 to 12 months after anterior cingulotomy [104,106]. Given the prevailing neurocircuitry model of OCD, these are all potential sites of therapeutic action. Of note, posterior cingulate cortex is well positioned to modulate activity within the OFC-caudate CSTC circuit [107–110]. Interestingly, a recent functional neuroimaging study of OCD demonstrated that presurgical activity within posterior cingulate cortex correlated with subsequent response after anterior cingulotomy [111]. Given the prevailing neurocircuitry model of MD, it might be more appealing to consider that lesions of dorsal ACC might produce disinhibition of pregenual ACC, which, in turn, might render patients more responsive to antidepressant pharmacotherapy after surgery. Alternatively, lesions of the cingulum might interrupt ascending influences of the amygdala on the dorsal compartment.

In the case of subcaudate tractotomy as well as bilateral orbitomedial leukotomy, the lesions are purportedly placed so as to interrupt fibers of passage connecting OFC and subgenual ACC to the thalamus. For orbitomedial leukotomy, the lesions might also disrupt amygdalofugal fibers to OFC and subgenual ACC [112]. In OCD, interruption of reciprocal projections between OFC and the thalamus would theoretically decrease reverberating (amplified) activity in the OFC-caudate CSTC, leading to reduced OCD symptoms. Likewise, in MD, reducing activity within the ventral compartment, such as directly lesioning subgenual ACC or OFC, would be hypothesized to reduce symptoms. A single case study of bilateral orbitomedial leukotomy has demonstrated reduced activity within OFC, ACC, the caudate, and the thalamus in a woman with OCD when comparing postsurgical with presurgical regional cerebral metabolism [113]. Such findings are confounded by symptomatic improvement of OCD, however, which characteristically yields this profile of attenuated hyperactivity throughout the circuit.

In the case of limbic leukotomy, lesions similar to those of anterior cingulotomy and subcaudate tractotomy are combined. Hence, this multisite operation would presumably combine the benefits (as well as the potential adverse effects) of the two

aforementioned procedures. A single case study of limbic leukotomy has demonstrated reduced activity within the caudate nuclei in a patient with OCD and TS when comparing postsurgical with presurgical regional cerebral oxygen metabolism [114]. Clinically, the patient exhibited improvement in both OCD and TS symptoms after limbic leukotomy.

In the case of anterior capsulotomy, lesions of the ventral portion of the anterior limb of the anterior capsule are likewise purported to interrupt OFC/subgenual ACC–thalamic connections. Moreover, the placement of these lesions may also compromise adjacent territories of the striatum. This can occur if the lesions interrupt fronto-striatal projections, if the lesions themselves impinge on the striatum, or if infiltration of edema surrounding the lesions encroaches on the striatum itself or on fronto-striatal projections. Again, for OCD, disruption of pathologic CSTC circuitry at the level of OFC-caudate or reciprocal OFC-thalamic communications could underlie the therapeutic effects of anterior capsulotomy. For MD, deactivation of subgenual ACC or disruption of interconnections among the elements of the ventral compartment is a plausible mode of therapeutic action for anterior capsulotomy. Interestingly, an MRI study of anterior capsulotomy for OCD and other anxiety disorders indicated that appropriate placement of lesions within the right anterior capsule was critical to subsequent therapeutic response [115]. Furthermore, functional imaging data from a small cohort of patients with severe anxiety disorders undergoing anterior capsulotomy demonstrated reductions in activity within orbitomedial frontal cortex from presurgical to postsurgical scans [116].

Summary and future directions

Neuroimaging research has helped to provide a progressively sound basis for constructing neurocircuitry models of OCD and MD. Still, our understanding of the pathophysiologic underpinnings of these disorders remains only tentative. Similarly, current knowledge regarding the neurobiologic consequences of contemporary psychiatric neurosurgical procedures is quite limited. Although extrapolation from nonhuman primate data can be informative, obtaining additional data from human subjects is essential to understanding the mechanisms by which psychiatric neurosurgery has its effects. Furthermore, advancing science in this domain is essential to optimizing neurosurgical treatment for psychiatric disorders in the future. It is foreseeable that progress in this area could lead to the identification of superior targets for ablative procedures, more effective selection of appropriate surgical candidates, and/or individualized interventions (eg, whereby targets are individually determined for each patient).

With the advent of deep brain stimulation, there are now opportunities to more flexibly (and reversibly) modulate activity within neural circuits of interest [117]. This promises the potential to advance our understanding of OCD and MD pathophysiology while systematically progressing toward improved neurosurgical treatments for the most severe and treatment-refractory forms of these diseases. Controlled treatment trials in this area should include a parallel neuroimaging component to maximize the clinical and scientific benefits derived from these efforts.

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