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Commentary

The role of cortical midline structure in diagnoses and neuromodulation for major depressive disorder

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Major depressive disorder and self-beliefs

Major depressive disorder (MDD) is a common and serious mental illness that severely affects people's psychosocial functioning and quality of life. Depression has been thought to be a major global cause of the burden of disease worldwide (Malhi & Mann, 2018; Vos *et al.*, 2017).

Maladaptive self-belief, such as negative self-evaluation, inappropriate self-blame, and self-criticism, is a core symptom of depression disorder (Auerbach *et al.*, 2014, 2015). Depressed individuals think about themselves in a negative way, and they are more sensitive to negative feedback (Giesler *et al.*, 1996), as well as the trend to recall negative self-related memories (Bradley & Mathews, 1983). The negative self-belief is associated with depression, which also significantly affects suicidal ideation and suicide attempts (Bhar *et al.*, 2008; Butter *et al.*, 2019; Nguyen *et al.*, 2019). Specifically, patients' negative constructs about self are highly associated with their suicidal ideation (Collett *et al.*, 2016).

The unique role of cortical midline structures in encoding self-beliefs

The most prominent brain structure that represents the self is the cortical midline structure (CMS). The CMS includes the ventral medial prefrontal cortex (PFC), the anterior cingulate cortex (ACC), the dorsal medial PFC, medial PFC (mPFC), and posterior cingulate cortex (PCC) (Northoff and Bermpohl, 2004).

Functional magnetic resonance imaging (fMRI) studies have revealed that the CMS including the mPFC and PCC encode self-related information (Feng *et al.*, 2018; Hu *et al.*, 2016; Kelley *et al.*, 2002; Northoff & Bermpohl, 2004) rather than others in the self-referential task. Specifically, the CMS exhibits greater blood-oxygen-level-dependent responses to personality trait judgments of the self (compared to others).

CMS and major depressive disorder

The resting-state functional connectivity based on CMS was found to be associated with negative self-belief (Fossati *et al.*, 2004). Consistently, one large sample size resting state study (resting-state fMRI data from 1300 patients with MDD and 1128 normal control participants) indicated that decreased FC in the CMS (mPFC and PCC) was found in recurrent MDD (Yan *et al.*, 2019). One possible explanation for the tight relationship between CMS and MDD is that the CMS serves as a critical structure in self-projection (Buckner & Carroll, 2007) and imagination that integrates information and beliefs to constitute a possible future episode (Benoit *et al.*, 2014). It has been theorized as the key region to represent concepts, meaning, value, and expectations related to personal well-being (Geuter *et al.*, 2017; Roy *et al.*, 2012). Thus, if individuals have negative self-reflection, it may further develop into depression with altered neural activity in CMS. Recent research (Li *et al.*, 2021) further strengthens the critical role of CMS in MDD. Researchers adopted surface-based morphometry to investigate cortical morphology in depression patients with and without suicidality. They found that the patients with suicidality showed significantly decreased sulcus depth in the mPFC, ACC, and PCC than patients without suicidality. Moreover, the sulcus depth in ACC and PCC could negatively predict the Hamilton depression score. Consistently, one empirical study revealed that the CMS processes the death-related information (Yanagisawa *et al.*, 2021). As the previous findings (Butter *et al.*, 2019; Collett *et al.*, 2016) show that negative self-belief indicates suicidal ideation, this further confirms the critical role of CMS in depression disorder.

Together, all the evidence suggests that the neural activity and cortical morphology in CMS can be critical biomarkers for the diagnosis of depression disorder. It could serve as a valid neuromodulation target for treating mental disorders.

Implications in psychiatry and future directions

So, what can we learn from the functions of CMS? First, brain activity in CMS is able to be a promising neuro-biomarker for the diagnosis of depressive patients. For example, previous task-based fMRI studies have unraveled how the CMS represents self-related information (Feng *et al.*, 2018; Kelley *et al.*, 2002), and the mPFC plays a large role in discriminating between positive and negative affect with self-relevance (Allaz *et al.*, 2021). Thus, researchers may collect and train the neural patterns that represent the self-beliefs in healthy populations, any patients who deviate from the normal pattern could be classified as high-risk groups for depression. Since researchers revealed the characteristics of the structure of CMS showed significant differences between healthy people and MDD, promisingly, it can further tell the difference between patients with suicidality and those not. In future studies, it will be necessary to combine multi-modal imaging data such

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as T1, resting-state, and task-based fMRI to train valid neuro-biomarkers from different perspectives. Another study found that the CMS also tracked the maladaptive self-beliefs in clinical high-risk psychosis (Cowan *et al.*, 2022), which indicates the CMS should be a potential candidate for trans-diagnosis across multiple mental disorders. Thus, future research should also consider more than one disorder to investigate the shared and distinct features among different disorders in CMS.

Second, since the CMS is sensitive, it is also important to utilize the neuro-biomarkers in CMS to detect the high-risk groups for depression. The current research (Li *et al.*, 2021) indicated that surfaced-based morphometry of CMS could dissociate MDD patients with suicidality from healthy and MDD patients without suicidality, which is promising, but if this study could associate the structural deficits in CMS with the depressive traits in high-risk populations of depression, this may provide an early diagnosis and effective prevention for depression disorder. Future research should consider the investigations on high-risk and undiagnosed groups.

Finally, beyond the traditional psychological intervention, neuromodulation tools such as transcranial magnetic stimulation, transcranial direct current stimulation, transcranial alternating current stimulation, and invasive close-loop electric stimulation have gained a lot of attention and importance in the last decade. Thus, the CMS could serve as a critical neuromodulation target to improve the positive beliefs about self and downregulate the negative bias. For example, researchers may explore the optimal parameters of transcranial magnetic stimulation to carry an electrical current pulse into the CMS to see how the negative self-beliefs improve. For individuals with treatment-resistant depression, if we can identify the specific neural oscillations or specific current by intracranial electroencephalogram for negative self-concepts, then we can further apply the transcranial alternating current stimulation to entrain the oscillations or invasive single-pulse electrical stimulation to alleviate the symptoms.

Conclusions

The central midline structures are critical for processing self-beliefs and have shown strong implications for MDD. It is promising to find novel and robust neuro-biomarkers in the CMS, as well as a new neuromodulation target to treat mental disorders such as depression and psychosis.

Author contributions

Xinyuan Yan (Conceptualization, Investigation, Project administration, Writing – original draft, Writing – review & editing)

Conflict of interests

The author declares no conflict of interest.

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