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COMMENTARY

The default mode network, depression and Alzheimer's disease

In our attempt to understand the brain basis of both normal and pathological brain function, the study of brain networks has been foundational (Bassett and Sporns, 2017). The brain is a complex network that can be studied at the level of the gene, protein, synapse, cell, circuit or system. In the search for the brain basis of the vast array of emotion, cognition, perception and action, much recent work has focused on network structures and processes that integrate brain function (Park and Friston, 2013). Clinical work on neural networks has been facilitated by the widespread availability of high-resolution magnetic resonance imaging (MRI) and rapid advances in computational tools. The application of graph theory analysis to covariance in structural (sMRI) and functional (fMRI) MRI data has resulted in better understanding of both the local- (segregated) and large-scale (global) organization of the brain. This organization provides the brain with its efficiency, robustness, adaptability and resilience.

Functional brain networks were initially studied in response to experimental tasks and stimuli (Biswal *et al.*, 1995; Friston, 2002). It was later observed that even when the brain is "at rest," with the individual lying in the scanner with their eyes closed, certain brain regions are active in organized synchrony (Greicius *et al.*, 2003). Subsequent work showed some brain regions that were active at rest to be synchronously deactivated when attention-demanding tasks were presented. This was labeled as the default mode network (DMN) (Raichle *et al.*, 2001). Anatomically, the DMN has been shown to comprise three main subdivisions: the ventral medial prefrontal cortex (VMPFC), the dorsal medial prefrontal cortex (DMPFC) and the posterior cingulate cortex (PCC) along with the adjacent precuneus and the lateral parietal cortex. The entorhinal cortex is sometimes associated with the DMN (Raichle *et al.*, 2001). These have also been referred to as the anterior and posterior elements of the DMN. The anterior elements have been shown to be involved in emotional processing (VMPFC) and self-referential mental activity (DMPFC), and the posterior elements in memory processes. Notably, these regions are anatomically distant from the sensory and motor systems of the brain (Smallwood *et al.*, 2021). The DMN has a central role in the large-scale functional organization of the brain. It interacts closely with other networks that exhibit patterns of connectivity at rest or during task performance (e.g. executive control, salience, dorsal attention, sensorimotor, visual and auditory networks).

Given the central role of the DMN in emotional and cognitive processes, it has been studied in relation to disorders such as depression (Borserio *et al.*, 2021; Drevets *et al.*, 1997) and Alzheimer's disease (AD) (Buckner *et al.*, 2008) using resting-state fMRI (rs-fMRI). Individuals with depression demonstrate significant differences in patterns of activity in the DMN, both at rest and during task activation (Broyd *et al.*, 2009). Several studies have shown failure of suppression of DMN activity in depressed individuals in response to a variety of stimuli, especially negative pictures (Sheline *et al.*, 2009), and this lack of inhibition was related to depressive self-focus in a meta-analysis (Lemogne *et al.*, 2012). Factors of observable activity in the DMN have been related to the core features of depression, and in a recent study using rs-fMRI, four neurophysiological biotypes of depression were identified which corresponded to clinical-symptom profiles with predominant anhedonia, psychomotor retardation, anxiety and insomnia (Drysdale *et al.*, 2017). Interestingly, a *resting-state hypothesis of depression* has been proposed (Northoff *et al.*, 2011) in which DMN is placed at the top of the organizational hierarchy in the neurodynamics of the attentional, emotional and sensory networks, and disturbance in the activity in components of the DMN and its ongoing functional connectivity forms the basis for the depressed state. Genetics, developmental factors, trauma, stress, neuroendocrine and other factors influence the connectivity patterns of the DMN and its vulnerability to a depressed state.

The PCC, a core posterior region of the DMN, is known to be affected early in AD as seen in functional imaging studies (Minoshima *et al.*, 1997). It has been shown that early in the AD process, there is decreased activity in the PCC and hippocampus, suggesting disrupted connectivity (Greicius *et al.*,

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2004). Activity in the DMN was suggested as a specific biomarker for early AD by these authors. Individuals with AD show abnormalities in other neural networks as well, and some of these have been related to cognitive function (Zhang *et al.*, 2020). Patterns of abnormal activity in the DMN in AD have been associated with risk of progression of AD from the stage of amnestic mild cognitive impairment (aMCI) to dementia, suggesting that they may be related to the underlying pathology (Koch *et al.*, 2015; Myers *et al.*, 2014).

The paper by Guan and colleagues (2021) is of much interest in this context. They used rs-fMRI to examine DMN activity in late-onset (geriatric) depression and AD as a strategy to examine the relationship between the two disorders and provide neurophysiological support for the hypothesis of depression as a risk factor for AD. Two groups of participants with depression were studied, both having remitted from depression, but with one group having persisting cognitive deficits to meet criteria for aMCI. The putative AD group was a clinically defined aMCI group. Using a seed-based approach (Lee *et al.*, 2013) to study the DMN, they found decreased functional connectivity between the PCC and the medial superior frontal gyrus (MSFG) in both depression groups and the aMCI group, and this was correlated with the severity of cognitive impairment in all three groups. The depression groups additionally had lower functional connectivity in other regions. The authors proposed that reduced functional connectivity between the PCC and MSFG, the posterior and anterior parts of the DMN, may be a feature common to depression and AD, thereby linking the two disorders.

The authors argue that disturbance in the DMN is a trait abnormality in depression, citing the literature on structural and functional abnormalities in neural circuits in depression involving the hippocampus, amygdala, anterior cingulate cortex and medial prefrontal cortex (Breukelaar *et al.*, 2019). This is consistent with the resting-state hypothesis of depression referred to above. The study does not, however, provide direct evidence of this, being a cross-sectional study, which used criteria for remission that do not ensure that complete recovery from the depressive state had occurred. Moreover, remission of depression is generally judged on the basis of mood and behavioral symptoms. It can be argued that recovery from depression does not necessarily follow a uniform trajectory across all domains, and the persistence of cognitive symptoms may suggest incomplete remission rather than a trait abnormality. It is also interesting that abnormalities seen in the remitted depression groups were more extensive than in the aMCI group. On the other hand, the two depression groups were similar to each other in their functional connectivity patterns. This further suggests that these may be state rather than trait abnormalities in depressed patients who had not completely remitted. Ideally, a longitudinal study is needed to resolve this issue.

Previous longitudinal studies have attempted to address this relationship. A study by Hill *et al.* (2020) examined the relationship between depressive symptoms and self-reported frequency of memory problems in the Einstein Aging Study over 11 waves of data. The memory problems and depressive symptoms were cross-sectionally correlated in older participants. Reports of decline over 1 year or 10 years covaried with depressive symptoms at any age. Lagged effects were found to show that depressive symptoms preceded future reports of self-reports of 10-year decline in memory (Yates, 2020). A multinational study from the COSMIC consortium showed an increase in the incidence of depression as the time to the diagnosis of dementia decreased, even though the rates of depression varied across different studies (Carles *et al.*, 2020), arguing for depression as a prodrome of dementia.

There are several caveats in using the findings of Guan et al. study to argue for depression as a prodrome of a neurodegenerative disorder. The demonstration of a functional similarity does not mean that the underlying pathobiology is the same. It is possible that the underlying basis of depression is neurochemical dysfunction which is quite distinct from the neuropathology of AD. This would lead to the conclusion that while the two functional abnormalities could well be additive in relation to cognitive impairment, one pathology would not necessarily promote the other. The conclusion that geriatric depression promotes AD pathology may therefore be erroneous. Another concern is the use of clinical aMCI as a proxy for AD in the absence of biomarkers. It is well recognized that only a proportion of aMCI progresses to AD dementia (Petersen *et al.*, 2009). The lack of biomarkers also raises the possibility that some of the depression group, especially those with aMCI, also had AD pathology, given the reports of depression as a prodromal feature of dementia (Carles *et al.*, 2020). It may therefore be more appropriate not to equate aMCI with AD in such a study.

This interesting study therefore provides further evidence for a network approach to associate neuropsychiatric disorders such as depression and AD. It does not however resolve the debate whether depression is a risk factor for dementia, or its

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prodrome, or both. It does not specifically address whether depression promotes the pathology of AD. It does, nevertheless, highlight the salience of some of these questions as we further our understanding of the brain basis of cognition, emotion and behavior, in health and in illness.

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