"Splitting of the Mind" Revisited: Recent Neuroimaging Evidence for Functional Dysconnection in Schizophrenia and Its Relation to Symptoms

Bleuler coined the term "schizophrenia" to capture the fragmentation and disintegration of the mind and behavior as the essence of the disorder (1). The splitting of thoughts, feelings, and actions was duly noted, but very few studies over the past century have addressed how and why these functions are dissociated in schizophrenia. Despite the robust evidence for the influence of emotion on cognition and vice versa (2, 3), the nature of these interactions and their role in psychotic symptoms are not clearly elucidated. Vast evidence indicates that emotion affects memory processes (4). Further, it has long been known that schizophrenia is associated with chronically elevated levels of anxiety and stress (5), and paranoid symptoms are hypothesized to be related to abnormal threat processing (6). As such, the influence of emotion on cognitive processes in schizophrenia deserves more attention than it has received.

In this issue of the *Journal*, a new study conducted by Satterthwaite et al. (7) addresses cognition-emotion interaction in schizophrenia with a functional magnetic resonance imaging (fMRI) experiment of an emotional face-recognition paradigm. Specifically, the participants performed an old versus new recognition memory task for neutral faces that they had previously seen with emotional expressions (threat versus nonthreat). Hence, this task required the participants to remember the faces while ignoring the past emotional context under which they learned them. The main hypothesis was that an imbalance between emotion and cognition would be manifested as an inverse relationship between limbic and cortical systems, such that as paranoid symptoms become more severe, limbic responses would predominate at the expense of cortical recruitment. Indeed, there was reduced activation of frontoparietal regions involved in recognition memory in individuals with schizophrenia relative to healthy comparison subjects, and this decreased activity was associated with increased symptom severity. Increased activity in limbic regions when processing faces that were previously displayed as threatening was associated with general symptom severity and paranoia in patients. Lastly, functional connectivity analysis suggests that in healthy participants, increased limbic activity was coupled with decreased activity in cortical regions, but this inverse relationship appears to be disrupted in schizophrenia. Overall, these findings suggest that abnormal processing of threat-related signals in the environment may exacerbate cognitive impairment in schizophrenia by tilting the cognition-emotion balance toward the limbic circuit, and they highlight the role of emotional context in cognitive deficits in schizophrenia. However, there are missing pieces in the puzzle with respect to functional connectivity analysis. First of all, it is unknown how increased or reduced functional connectivity translates to behavior, and, second, it is equally unclear how reduced cognitive capacity might influence emotion. In other words, the authors have addressed "cognition versus emotion" from one end. It would be informative to consider traversing the opposite direction as well. Nevertheless, this work highlights the importance of examining cognitive and emotional processes in tandem.

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One methodological innovation that distinguishes this work is that Satterthwaite et al. examined neural activity during the processing of stimuli that were *previously* associated with threat; that is, they investigated the effects of past emotional context on current cognitive demand for recognition memory. Positive symptoms have been hypothesized to arise from the weakening of the influence of stored regularities (i.e., memory) on the interpretation of current ongoing events (8). Another innovative report also in this issue of the *Journal* addresses the role of memory in psychosis. Diederen et al. (9) provide evidence for the potential role of memory in sensory experiences (i.e., hallucinations). Patients with psychosis were instructed to squeeze a balloon to indicate when they were experiencing an auditory verbal hallucination during fMRI. In a clever and sophisticated analysis, they investigated brain activation both *prior* to and during auditory hallucinations to elucidate the conditions that lead to hallucinatory experience. During hallucinations, patients showed increased activation of the expected neural network of language-related regions. Interestingly, the authors also observed a pronounced deactivation of the parahippocampal gyrus *prior* to experiencing an auditory hallucination. Given the central role of the hippocampus in memory recollection, the authors argue that disinhibition of the parahippocampal gyrus via dopaminergic innervations triggers activity in language-related networks, and auditory verbal hallucinations could result from re-experiencing old memories.

In healthy individuals, there is a continuous integration of the past, present, and future that helps forge a sense of unitary self across time. This unbroken mental landscape appears to be disrupted in psychosis (10), which is reflected in the results of Satterthwaite et al. and Diederen et al. One is also reminded of the neuropsychological theory of psychotic symptoms proposed by Gray et al. (11) that addressed how structural abnormalities in limbic regions cause hyperactivity in the ascending mesolimbic dopamine pathway, which in turn disrupts a particular cognitive process, eventually leading to psychosis. The particular disrupted cognitive process was conceptualized as integrating past experience (stored regularities) with current stimulus processing (8). It was posited that hallucinations are essentially intrusions of unexpected or unintended information from long-term memory due to unstructured sensory input. By analyzing cortical and subcortical brain activity of psychotic individuals prior to and during florid auditory verbal hallucinations, Diederen et al. provide powerful data that directly address the psychological and neural origins of hallucinations. As Gray's model would predict, auditory verbal hallucinations were triggered by disinhibition of memory-related limbic regions. Satterthwaite et al. also report abnormal neural activity in limbic regions in patients with schizophrenia during face recognition that is modulated by previous affective experience with the stimuli. In patients, prior associations with threat interfered with current processing of the stimuli, indexed by greater limbic activity when viewing faces previously shown as threatening. Consistent with Gray's model, the degree of interference from these old memories (i.e., affective interference) at the level of brain function was associated with a greater degree of paranoia.

More generally, both studies are noteworthy in their consideration of dysconnectivity at the level of both behavior and brain—a dysconnect between past events and current perception, between emotion and cognition, and between activity in brain regions that support these functions. Note that we use the terminology adopted by Stephan et al. (12) (dysconnectivity versus disconnectivity) to refer to abnormal, rather than necessarily decreased, functional interactions. Indeed, this idea of dysconnectivity has been noted in the earliest clinical observations of schizophrenia (1), and it is directly or indirectly represented in several more recent theories that incorporate the pathophysiology and symptomatology of the disease. Stephan et al. formally described this dysconnection hypothesis, citing evidence that abnormal *N*-methyl-D-aspartic acid-dependent synaptic plasticity results in abnormal functional coupling between brain regions in schizophrenia.

To conclude, these two new studies shed further light on the neural underpinnings of psychosis, providing advanced insights into the physiological nature of positive

symptoms. Further, their consideration of the influence of prior experience on current symptoms contributes new functional evidence that speaks to earlier theories that were based largely on clinical observations. Finally, these findings lend support to the idea of dysconnection in schizophrenia—between regions mediating emotion and cognition and between memory and perception. In this way, the idea of "split mind" becomes relevant in an updated context, and these studies address the mechanism by which splitting of the psyche potentially occurs.

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