the classification system could be updated to incorporate new knowledge. A shift to a more nuanced, personalized disease classification of dementia at the earliest possible stage of disease might revolutionize therapeutics.

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Cortical dopamine dysregulation in schizophrenia and its link to stress

This scientific commentary refers to 'Cortical stress regulation is disrupted in schizophrenia but not in clinical high risk for psychosis', by Schifani *et al.* (doi:10.1093/brain/awy133).

Dysregulation of the dopamine system is a well-established component of schizophrenia pathophysiology, with regional differences in dopamine targets thought to shape disease symptoms. Increased presynaptic striatal dopamine synthesis and release are among the most consistent findings in patients. These alterations seem to occur early in the disease as they are also observed in prodromal subjects that are at clinical high risk (CHR) for developing schizophrenia. To date, PET studies have focused largely on the striatum, but it has additionally been postulated that dopamine transmission is decreased in the prefrontal cortex (PFC) in schizophrenia. Dopamine in the PFC plays a key role in modulating cognitive and executive functions such as attention, working memory, and decision-making, all of which are impaired in schizophrenia. Earlier PET studies were limited to the striatum because the available radioligands, such as ^{11}C-raclopride, did not provide an adequate signal-to-noise ratio to quantify $D_{2/3}$ receptors in extrastriatal regions, such as the cortex, where the expression of $D_{2/3}$ receptors is much lower. However, more recently, the development of high-affinity dopamine $D_{2/3}$ receptor PET radioligands, such as ^{11}C-FLB457 and ^{18}F-fallypride, has made it possible to image changes in dopamine release in the human cortex. In this issue of *Brain*, Romina Mizrahi's group examines whether exposure to acute psychosocial stress leads to altered cortical dopamine release in patients with schizophrenia and in individuals at CHR for psychosis (Schifani *et al.*, 2018).

Prior to the report by Schifani *et al.*, only one other study had examined PFC dopamine release in patients with schizophrenia. Using the high-affinity $D_{2/3}$ radioligand ^{11}C-FLB457, which is superior to the other cortical $D_{2/3}$ radioligand ^{18}F-fallypride (Narendran *et al.*, 2009), Slifstein *et al.* (2015) observed blunted cortical dopamine release in response to an amphetamine challenge in patients. Various studies have suggested that abnormal dopamine synthesis and release also occur in CHR and seem to predict

conversion to schizophrenia. However, it is worth noting that the Schifani *et al.* study is the first to investigate cortical dopamine function in individuals at CHR for psychosis.

Mizrahi's group were pioneers in investigating dopamine release in response to stress in schizophrenia. Mizrahi *et al.* (2012) provided the first evidence of greater striatal dopamine release in response to psychosocial stress in CHR and in patients with schizophrenia. They also showed that migration, a major risk factor for schizophrenia, is associated with abnormal striatal dopamine function, by revealing elevated striatal stress-induced dopamine release in immigrants and their children (Egerton *et al.*, 2017). They now switch their attention to stress-induced dopamine release in the PFC of patients with schizophrenia and CHR individuals.

Stress is known to play a major role in susceptibility to mental disorders in general, including schizophrenia. Exposure to stressors (e.g. childhood trauma, ethnic minority status, social disadvantage, urbanicity) is associated with an increased risk for psychosis, and is known to increase emotional reactivity. It may also sensitize the dopamine system, increasing the intensity of psychotic experiences (Howes *et al.*, 2017). Although stress can be regulated by multiple regions throughout the brain, the PFC is proposed as a primary integrator of the stress response. PFC dysfunction is thought to impair an individual's ability to regulate their stress response, rendering them more susceptible to the deleterious effects of stress and, consequently, contributing to the emergence of psychiatric disorders such as schizophrenia (Gomes and Grace, 2017). Importantly, reduced prefrontal cortical activity is also associated with elevated striatal dopamine function in patients with schizophrenia and individuals at CHR for psychosis (Meyer-Lindenberg *et al.*, 2002; Fusar-Poli *et al.*, 2011) and blunted cortical dopamine release is likely to result in an augmented striatal release of dopamine (Howes *et al.*, 2017).

Schifani *et al.* report an abnormal cortical stress-induced dopamine release in patients with schizophrenia that was not observed in individuals at CHR. In brief, antipsychotic-free patients, individuals at CHR and healthy controls underwent two PET scans, one while performing a sensory motor control task (control scan) and another while performing a validated psychological stress task—the Montreal Imaging Stress Task (stress scan)—to elicit dopamine release. Dopamine release was measured using ^{11}C-FLB457 PET, through quantification of the competition between endogenous dopamine and ^{11}C-FLB457 for $D_{2/3}$ binding in the medial PFC and dorsolateral PFC. Stress-induced dopamine release was quantified as the percentage change in binding potential (BP_{ND}) between stress and control sessions (ΔBP_{ND}). Salivary cortisol, an index of stress, was assessed throughout the tasks and its relationship with dopamine release examined.

Consistent with previous studies, patients with schizophrenia and individuals at CHR showed higher chronic stress scores, a greater number of stressful life events and displayed higher anxiety levels than controls. Changes in salivary cortisol confirmed that the stress paradigm was effective in inducing stress states. But although patients with schizophrenia and individuals at CHR have been reported to show greater responsivity to stress, changes in salivary cortisol did not differ between the groups, including during the stress scan. In contrast to the findings of their previous work showing increased striatal stress-induced dopamine release in CHR individuals and patients with schizophrenia versus controls (Mizrahi *et al.*, 2012), Schifani *et al.* failed to find group differences in cortical stress-induced dopamine release. However, the percentage change in dopamine release in the medial PFC and dorsolateral PFC between the control and stress tasks was positively associated with the cortisol response to stress in both CHR individuals and controls. This suggests that stress leads to increased cortical dopamine release, a finding that is also consistent with animal data. Interestingly, this correlation between cortical dopamine release and salivary cortisol in response to stress was absent in patients with schizophrenia. These findings thus provide the first evidence of disrupted cortical dopamine-stress regulation in schizophrenia.

In addition to the involvement of cortical dopamine signalling in cognitive function, dopamine in the PFC plays an important role in integrating aspects of the stress response. Stress-induced dopamine release in the rodent medial PFC attenuates subcortical dopamine overstimulation (King *et al.*, 1997), and the medial PFC helps regulate amygdala responses to stress (Rosenkranz and Grace, 2001). Blunted stress-induced dopamine release in the PFC may thus cause an exaggerated stress response subcortically in patients with schizophrenia. This may impair the ability of these individuals to respond appropriately to stress, which has been linked to an increased risk of relapse.

The findings from Schifani *et al.* are consistent with the study by Slifstein *et al.* (2015), in which patients with schizophrenia showed blunted amphetamine-induced cortical dopamine release. Another important feature of the study by Schifani *et al.* is that, although ^{11}C-FLB457 has been validated as a tool to image amphetamine-induced dopamine release in the frontal cortex (Narendran *et al.*, 2009), this is the first study to demonstrate that this radioligand also provides reliable quantification of cortical dopamine release induced by stress.

Blunted cortical dopamine release in schizophrenia in response to stress contrasts with the well-replicated increase in dopamine release in the striatum. While individuals at CRH also show increased striatal stress-induced dopamine release (Mizrahi *et al.*, 2012), in the current study they did not show the abnormal (blunted) cortical stress-induced

dopamine release that was evident in patients with schizophrenia. These findings argue against the idea that blunted cortical dopamine release leads to increased striatal dopamine synthesis and release (Howes *et al.*, 2017). Indeed, in rodent models of striatal D2 overexpression (Simpson and Kellendonk, 2017), increased striatal dopamine transmission was sufficient to impact prefrontal cognitive processes, suggesting that the relationship may work in the opposite direction. In individuals at CHR, secondary analyses revealed that stress-induced dopamine release was negatively associated with several measures of distress as well as cortisol levels during the stress scan. However, these associations were absent in schizophrenia. A longitudinal study following up the CHR individuals for a sufficient period would provide crucial information on how these findings could relate to subsequent transition to full-blown psychosis.

In sum, further studies will be critical to obtain a better understanding of the mechanisms that contribute to blunted cortical dopamine transmission in schizophrenia, as well as to the contrast between increased striatal dopamine release versus reduced cortical dopamine, and the clinical relevance of these phenomena. Nonetheless, this manuscript has provided unique insights into the relationships between cortical dopamine, stress and striatal dopamine function, in a manner that may substantially alter our understanding of their functional interdependence.

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