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P. Szeszko
Hofstra Northwell School of Medicine

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Aggression in Schizophrenia and its Relationship to Neural Circuitry of Urgency

PHILIP R. SZESZKO, Ph.D.

Center for Psychiatric Neuroscience, The Feinstein Institute for Medical Research, Manhasset, N.Y.; the Division of Psychiatry Research, Zucker Hillside Hospital, North Shore-LIJ Health System, Glen Oaks, N.Y.; and the Departments of Psychiatry and Molecular Medicine, Hofstra North Shore–LIJ School of Medicine, Hempstead, N.Y

Aggression is a major societal health concern that significantly affects individuals with psychiatric disorders and their families, treating clinicians, and mental health aides, leading to substantially higher health care costs and stigmatization. Aggression can be defined as the intent to injure another individual using either physical or psychological means, and it has the potential to lead to violence when left unchecked. The Global Burden of Diseases, Injuries, and Risk Factors Study (1), which investigated mortality from causes of death, indicated that interpersonal violence accounted for 5.2% of global deaths for males and 1.6% of global deaths for females among individuals ages 15–49 years in 2010. Although the majority of individuals with psychiatric disorders are neither aggressive nor violent, a small subgroup of patients may be more violent compared with the general population; however, the overall proportion of violence that can be attributed to this subgroup is low (2). Moreover, aggressive and violent behavior have been linked to a number of factors other than psychosis, including childhood adversity (3), substance use (4), and conduct problems in childhood (5).

In a recent meta-regression of 110 studies (6) investigating 45,533 individuals with psychotic disorders, 8,439 (18.5%) were determined to be violent, with impulsivity identified as one of the key risk factors. The brain regions that play a role in impulsive behavior are a critical area for research and are beginning to be understood using neuroimaging techniques such as resting-state functional MRI (fMRI). In a study that examined the relationship between impulsivity and brain modularity, Davis et al. (7) found that prefrontal regions associated with the regulation of control, including the medial and lateral aspects of the prefrontal cortex, were “isolated” from subcortical regions that play a role in appetitive drive among individuals with high impulsivity. In contrast, these brain regions tended to cluster together among less impulsive individuals. Much less is known, however, regarding the interrelationship among brain regions contributing to impulsivity and its role in aggression among individuals with psychotic disorders, although there is some evidence that greater impulsivity is associated with more activation within the right ventrolateral prefrontal cortex during a response inhibition task (8). Although impulsivity

Address correspondence to Dr. Szeszko (szeszko@lij.edu).

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can play a role in aggressive behavior, the construct of impulsivity is multifaceted and may not capture core aspects of phenomenology.

The Urgency, Premeditation, Perseverance and Sensation-Seeking Scale subdivides impulsivity into specific domains, and it may be a useful tool for furthering our understanding of impulsivity among individuals with psychotic disorders. In particular, the construct of urgency (9, 10) may play an important role during the experience of significant heightened emotion that is distinct from the impulsive behavior that contributes to aggression, violence, substance use, and gambling disorders, among others. Urgency refers to acting rashly when experiencing strong affect and is subdivided into positive (for strong positive affect) and negative (for strong negative affect) urgency. Thus, the investigation of urgency could enhance our understanding of impulsivity through the use of affective dimensions. Although there is an extensive literature regarding the role of impulsivity in schizophrenia, the study of urgency and its underlying neural circuitry has not yet been integrated into current research paradigms in psychotic disorders.

In this issue of the *Journal*, Hoptman et al. (11) investigate the construct of urgency in relation to aggression in individuals with schizophrenia or schizoaffective disorder and its underlying neural circuitry. Their findings indicate that both positive and negative urgency were significantly elevated in patients compared with healthy volunteers in the absence of group differences in premeditation, perseverance, and sensation-seeking. Moreover, using mediation analysis, urgency measures uniquely accounted for a significant proportion of the variance in aggression, over and above the effects of clinical group. At the neural level, they report that greater urgency was associated with lower cortical thickness as well as lower functional connectivity within the medial/lateral orbitofrontal, inferior frontal, and rostral anterior cingulate cortical regions. This is important given that these regions have been linked to response inhibition, cognitive control, and conflict monitoring. It is also particularly noteworthy that many of the networks that associated positively or negatively with urgency were themselves inversely correlated, suggesting that different networks “compete” to regulate behavioral variability related to urgency in schizophrenia. It is therefore conceivable that an inability to differentially engage these networks, as well as difficulty modulating their interaction, could contribute to increased urgency and aggression in schizophrenia. These competing networks may be linked to positive and negative urgency through aberrant function and structural deficits comprising ventral prefrontal regions. Thus, a major strength of the Hoptman et al. neuroimaging study is the use of both structural and functional imaging to interrogate brain circuits that play a role in urgency.

The present study also builds on prior research by Hoptman and colleagues supporting a role for the orbitofrontal cortex in the neurobiology of aggression and impulsive behavior. Previously (12), these authors observed that lower fractional anisotropy and higher trace, putative measures of white matter integrity obtained using diffusion tensor imaging, within the right inferior frontal white matter were associated, respectively, with higher motor impulsiveness and aggression among men with schizophrenia. Subsequently, using resting-state fMRI they identified lower functional connectivity within a ventral prefrontal cortex-amygdala circuit and self-reported aggression (13).

There are several caveats to the study that should be acknowledged. Patients were chronically ill and receiving antipsychotic medications; studies investigating the neural circuitry of urgency in individuals with first-episode psychosis with minimal prior antipsychotic treatment, as well as other disorders (14) falling along an impulsivity spectrum within the context of the Research Domain Criteria project, would be useful. It is known that gender plays an important role in mediating aggression and, given that the patients in the study were predominantly male, future research needs to be extended more broadly to female individuals. As the authors acknowledge, the scales were obtained from self-report measures, and thus family- or clinician-rated assessments could provide convergent validity for the behavioral assessments.

There are several potentially important future directions from this line of research. An important implication is that impulsivity reflects both positive and negative urgency and occurs within a framework of affectively laden constructs in contrast to a lack of premeditation, lack of perseverance, or sensation-seeking. Such research can be used to further develop a framework to link the neurobiology of impulsivity with the construct of urgency (15). Moreover, these studies could potentially constrain hypotheses regarding underlying neurobiological processes in order to identify novel therapeutic targets, especially when combined with imaging genomics, given that some genes (e.g., catechol-*O*-methyltransferase) have been strongly implicated in aggression among individuals with schizophrenia (16).

In sum, the Hoptman et al. study highlights the underappreciated role of urgency in aggression among individuals with schizophrenia and the concomitant underlying neural circuits that may mediate this relationship. For clinicians treating individuals with schizophrenia, it is a reminder that impulsivity and urgency may be risk factors for aggressive behavior.

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