Biological Psychiatry: Celebrating 50 Years

Looking Under the Hood of Convergent Behavioral Deficits in Schizophrenia and Autism

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Autism spectrum disorder (ASD) and schizophrenia are two neurodevelopmental disorders sharing a complex, overlapping history (1). After an initial period during which both phenotypes were subsumed within one diagnosis, for many decades ASD and schizophrenia have been conceptualized as quite divergent disorders. Indeed, the onset of ASD occurs during early childhood, and schizophrenia usually does not emerge until adolescence or early adulthood, making the developmental trajectories distinct. However, genetic studies point to an overlap between ASD and schizophrenia, with many common gene variants implicated in both disorders and several genetic disorders associated with risk for both clinical manifestations (2).

Clinically, several key features of ASD and schizophrenia converge (3). Both disorders are characterized by social difficulties, limited nonverbal communication, abnormal sensory experiences, and atypical language. Experimental behavioral research reflects this overlap: studies in both schizophrenia and ASD have identified difficulties in face processing, emotion recognition, theory of mind, empathy, executive functioning, basic sensory perception, and multisensory integration (4). In both disorders, researchers have posited that deficits in low-level (e.g., sensory) functioning may drive higher-order (e.g., social) aspects of the phenotype. And yet, there are ways in which the two disorders are quite different: in addition to the developmental timing of onset, most individuals with ASD do not have hallucinations or delusions, and most individuals with schizophrenia do not have motor mannerisms or markedly atypical language development and/or use (e.g., echolalia or verbal rituals) in childhood.

Features shared across schizophrenia and ASD could emerge in two distinct, though non–mutually exclusive, ways. First, they could represent deficits in transdiagnostic processes, where central underlying biological disruptions result in behavioral abnormalities and clinical symptoms that span multiple diagnostic categories—in this case, ASD and schizophrenia (5). This possibility is in line with the Research Domain Criteria framework (6). Second, overlapping symptoms could represent nonspecific features that appear to be similar at the level of clinical observation and behavioral experimentation but in fact result from quite different underlying neuropathology. In this many-to-one scenario, the basic biology between the disorders differs, but the resulting symptoms are less easily distinguished.

Until quite recently, most experimental and neuroimaging research in schizophrenia and ASD was done separately. In parallel, ASD and schizophrenia researchers have been probing social functioning, sensory processing, theory of mind, and cognition (4). In looking for underlying neural abnormalities, they have been testing for alterations in neural connectivity, excitatory/inhibitory neurotransmitter balance (7), resting-state brain activity, and predictive coding processes. However, though similar questions have been asked across ASD and schizophrenia—often using similar tasks and tools—methodological and analytical differences across studies have limited the extent to which findings in one disorder could be compared with those in the other. Therefore, the degree to which apparent clinical and behavioral features of ASD and schizophrenia truly converge has remained unclear.

In this issue of *Biological Psychiatry*, Martínez *et al.* (8) take an important step forward in collecting the integrated dataset necessary to begin reconciling findings across schizophrenia and ASD. Groups of adult participants with schizophrenia and ASD were recruited and compared with healthy control subjects. The study examined two aspects of visual perception—motion sensitivity and face emotion recognition (FER)—arguing that lower-level deficits in motion detection could contribute to deficits in processing more visually complex FER stimuli. Impaired FER is a routinely recognized deficit across both ASD and schizophrenia; motion perception deficits also span both disorders, though in ASD the case is less clear (9). In the present sample, however, Martínez *et al.* (8) detect behavioral deficits in both schizophrenia and ASD groups, relative to control subjects, in both FER and motion detection.

Taking a Research Domain Criteria approach in measuring basic functions across several units of analysis, the study goes on to examine electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) signatures of motion perception. Martínez *et al.* (8) tested whether neural differences in processing of these simple, nonsocial stimuli contribute to variance in performance on the higher-order FER task. In each trial presented during EEG, vertical gratings first appeared static on the screen, then drifted rightward, then became static again and were contrast-reversed for the remainder of the trial. During MRI, both neural response to expanding and contracting concentric rings and resting-state functional connectivity were measured. Finally, machine learning was used to test whether EEG and fMRI variables could discriminate among groups.

Martínez *et al.*'s results (8) revealed that despite similar behavioral performance between ASD and schizophrenia groups on both motion sensitivity and FER tasks, neural response during lower-level visual processing and at rest differed in several key ways (Figure 1). The onset of static visual gratings evoked reduced theta power in schizophrenia but increased theta power in ASD relative to control subjects. In ASD, this increase corresponded with worse FER but not worse motion sensitivity. In schizophrenia, theta was unrelated to performance on either behavioral task. Alpha event-related

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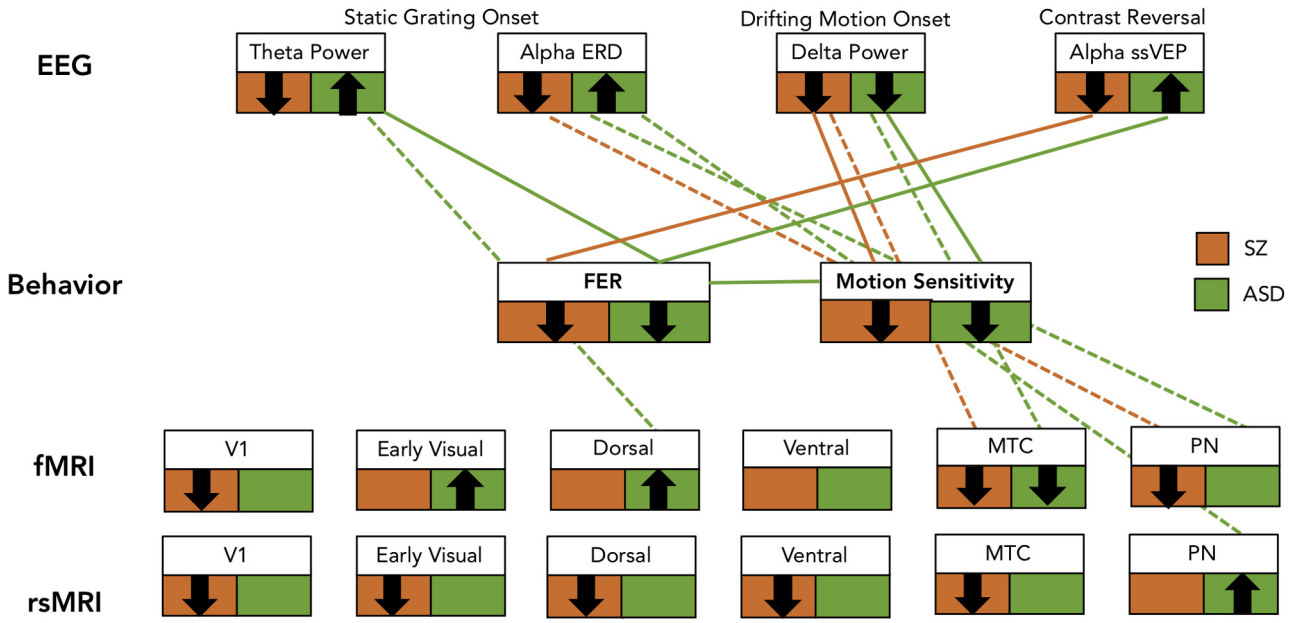

Figure 1. Summary of key findings by Martínez *et al.* (8) across behavioral, electroencephalography (EEG), and magnetic resonance imaging (MRI) measures. Findings in schizophrenia (SZ) are shown in orange; findings in autism spectrum disorder (ASD) are shown in green. Arrows pointing down reflect decreased behavioral performance or brain activity relative to control subjects. Arrows pointing up reflect increased/enhanced brain activity relative to control subjects. Colored boxes with no arrows indicate no difference between clinical groups and control subjects on associated metrics. Solid lines between boxes represent significant correlations between EEG measures and behavioral task performance in the group represented by the color of the line. Dashed lines between boxes reflect significant correlations between EEG and MRI measures. ERD, event-related desynchronization; FER, facial emotion recognition; fMRI, functional MRI; MTC, middle temporal cortex; PN, pulvinar nucleus; rsMRI, resting-state MRI; ssVEP, steady-state visual evoked potential; V1, primary visual cortex.

desynchronization (ERD) after stimulus onset was also reduced in schizophrenia but enhanced in ASD. However, alpha ERD was unrelated to behavioral task performance in any group. With the onset of drifting motion, reduced evoked delta power was observed across both ASD and schizophrenia, yielding the first convergent neural finding. Across both schizophrenia and ASD, reduced delta power corresponded with lower behavioral motion sensitivity but not with FER performance. In the final EEG-related analysis, relative to control subjects, 10-Hz steady-state visual evoked potential power to contrast reversals was reduced in schizophrenia but increased in ASD. Across groups, steady-state visual evoked potential was associated with FER but not motion sensitivity.

MRI results during the motion task revealed reduced primary visual cortex (V1), middle temporal cortex (MTC), and subcortical pulvinar nucleus (PN) activation but typical early visual and dorsal activation in schizophrenia. In ASD, MTC activation reductions paralleled those in schizophrenia; however, there were no V1 or PN activity reductions, and activation was enhanced relative to controls in early visual and dorsal regions. Resting-state analyses showed that relative to control subjects, patients with schizophrenia had reduced connectivity of the V1, early visual, dorsal, ventral, and MTC regions, but intact PN–cortex connectivity. In ASD, there were no cortical connectivity reductions, but PN–cortex connectivity was enhanced.

Martínez *et al.* (8) report several relations between EEG and fMRI data, highlighting the benefit of collecting both data types. Across groups, delta power to motion onset during EEG was associated with MTC activation to expanding/contracting stimuli during fMRI. In ASD, enhancement of dorsal activity during motion perception correlated with increased theta power to static stimulus onset. In both clinical groups, alpha ERD to visual stimulus onset was associated with PN activity during motion perception. Alpha ERD also correlated with PN–cortex connectivity in ASD. Classification analyses revealed that combined MRI and EEG variables yielded better classification of clinical participants than did either set of variables alone.

Finally, returning to the question of contributions of low-level visual processes to FER deficits, different patterns emerged across diagnostic groups. In ASD, behavioral motion sensitivity and theta activity to static stimulus onset were significant predictors of FER. In contrast, in schizophrenia, FER was best predicted by alpha activity during EEG, V1 activation during motion perception, and mean PN connectivity at rest. This set of findings highlights that although FER is deficient across both disorders, neural contributors to these deficits differ between clinical groups.

This cross-diagnostic study measuring visual perception across two basic functions and multiple units of analysis makes an important contribution in revealing a scenario in which distinctly different patterns of brain alterations across ASD and schizophrenia yield behaviorally similar performance deficits in a key social function. Such information is critical in considering treatment options; if the biology underlying similarly manifesting core deficits is fundamentally different in schizophrenia and ASD, then it cannot be assumed that a treatment effective in one disorder will readily be translatable to the other. Indeed, while the use of dissociable EEG and fMRI

variables to predict diagnostic category, as done in Martínez *et al.*'s classification analyses (8), is alluring, the more likely clinical application of these findings may be toward developing targeted treatments to address directionally different brain-based alterations.

Several questions remain unanswered. First, the extent to which lower IQ, reduced education attainment, lower task engagement during EEG, and significant psychotropic medication use may have contributed to findings of reduced brain activity in schizophrenia would be best parsed in larger studies with better matched groups that might include subsets of medication-naïve schizophrenia patients and/or ASD patients taking antipsychotic medications for irritability. Second, the discrepant findings across disorders is intriguing in light of the increased rates of psychosis in ASD and of ASD in schizophrenia (10). Though Martínez *et al.* (8) excluded patients with dual ASD and schizophrenia diagnoses, findings from this subset would be interesting to explore. This type of work could offer particular clues into brain-based features that, when observed in young individuals with ASD, could predict vulnerability to future psychosis diagnosis. Finally, this study approach ought to be applied to assessing contributions of other neural processes (e.g., in the social brain) to FER abilities and to extending this work to other shared deficits between ASD and schizophrenia. Such future work would enable continued headway to be made toward better understanding the degree to which manifest symptoms across schizophrenia and ASD converge and diverge neurobiologically.

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Article Information

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