CORRESPONDENCE

Neurobiology of Emotional Dysfunction in Schizophrenia: New Directions Revealed Through Meta-Analyses

To the Editor:

Affective dysfunction is a prominent feature of schizophrenia psychopathology. Behavioral studies converge on several distinct aspects of emotional dysfunction, namely, 1) emotion expression (1–3); 2) recognition of facial expressions and emotional classification (4,5); and 3) anticipation of hedonic experience (6,7). However, precise neural deficits across these domains remain obscure. For a decade, neuroimaging studies have probed affective dysfunction in schizophrenia under a variety of conditions, but no clear consensus emerged. These equivocal findings revealed a clear need for meta-analytic summaries of reported effects: over the past year, three groups have independently conducted meta-analyses of the functional neuroimaging literature of emotional processing in schizophrenia (8–10), with somewhat different, but complementary goals: 1) Li *et al.* examined evidence for differences in activation peaks across studies of facial emotion; 2) Anticevic and colleagues quantified the magnitude of activation differences in the amygdala; and 3) Taylor and colleagues expanded the search across all cortical and subcortical regions.

The three studies highlight how slight variation in meta-analytic strategies can produce both complementary and divergent results. For instance, Li and colleagues reported reduced amygdala and fusiform gyrus activity in schizophrenia in response to emotional faces. However, they employed a version of activation likelihood estimation that samples activation peaks across studies, but treats each peak as independent. Such results can be biased by studies that report a greater number of peaks (11), although a recent modification of activation likelihood estimation corrects this problem (12). In contrast, the region of interest–based effect-size analysis employed by Anticevic *et al.* allowed in-depth probing of a given region—the amygdala—and permitted a search for variables that moderate the magnitude of observed effects in this region. This study confirmed reduced amygdala activation in schizophrenia but did not examine differences elsewhere in the brain. The most recent study, that by Taylor and colleagues, expands on the aforementioned strategies via multilevel kernel density analysis, a tool designed for voxelwise examination of task contrasts (11). Although this approach does not measure the magnitude of between-group effects in a given study, it can reveal regions that show consistent differences across the entire brain, while overcoming peak bias. Such an approach has the potential to provide a window on novel aspects of compromised circuitry involved in emotional processing in schizophrenia.

The overall pattern of results reported by Taylor and colleagues was critical in that it ruled out the possibility that all differences in the literature involve hypoactivation in response to emotional probes in schizophrenia—a proposed pattern that has been dominating the literature since the earliest reports of reduced amygdala signals (13). Rather, Taylor and colleagues reported several foci of "hyperactivity" for patients relative to control subjects. This finding suggests that not all neural correlates of emotional processing deficits in schizophrenia can be thought of as reduced computations in specific brain regions (e.g., amygdala) but rather involve more complex patterns. Furthermore, Taylor and colleagues' findings reveal how critical it is to consider the complexity of specific aspects of emotional processing abnormalities in schizophrenia and the need for close examination of different components of affective processing that may be differentially impaired in this illness. In particular, they illustrate potential differences between explicit and implicit emotional tasks, as well as between emotion perception and emotion experience—dichotomies highlighting that patients may show abnormalities in some aspects of emotional processing but not others. This complex picture of neural deficits is consistent with behavioral findings that suggest intact emotional experience, but impaired affective appraisal, in schizophrenia (14). An important caveat, acknowledged by the authors, is that these contrasts involved a small sample of studies and thus should be treated as provisional interim findings. Nevertheless, one important possibility with regard to explicit versus implicit findings is that patients may be able to engage compensatory regions during effortful emotional appraisal (i.e., explicit processing), which results in increased activity in regions such as the precentral gyrus, temporal cortex, and the cuneus. In that sense, Taylor and colleagues' results also suggest that it is paramount to consider affective dysfunction in schizophrenia as an abnormality involving distributed neural circuitry (certainly extending beyond the amygdala). Therefore, the novel results generated by Taylor and colleagues can serve as seeds to investigate deficits in broader networks underlying emotional dysfunction symptomatology, presenting new opportunities for extending our understanding of emotional pathology in schizophrenia.

Although these findings are compelling, the possibility that patients "overrecruit" regions typically associated with emotion processing in response to neutral stimuli remains an open question. Because Taylor and colleagues focused on contrasts of activity between valenced and neutral conditions, it may be possible that foci of "underrecruitment" are actually reflecting overrecruitment in the neutral condition for patients, a likely possibility given that Anticevic et al. found that only studies using neutral stimuli observed underrecruitment of the amygdala (8). It will be critical for future experimental and meta-analytic reports to disambiguate this possibility fully. Indeed, in our recent experimental work involving visual perception of complex emotional and neutral scenes, we failed to observe amygdala overrecruitment in the neutral condition (15); however, it may be possible that aberrant overrecruitment emerges for social stimuli (i.e., faces) that may be particularly survival-relevant but not necessarily perceived as "valenced" or "salient" in healthy individuals. Another unresolved aspect regarding the neurobiology of emotional dysfunction in schizophrenia is the extent to which patients show disturbances in processing positive affect. Meta-analyses in healthy adults have pinpointed distinct circuits involved in processing positive versus negative valence (16), but these advances have yet to be fully extended to schizophrenia research.

It is clear that recent meta-analytic investigations have the capacity to focus our efforts in understanding emotional pathology in schizophrenia. Perhaps a direction for the future involves accelerating progress by capitalizing on state-of-the-art automated meta-analytic tools developed in basic cognitive neuroscience (17) and to harness such tools toward understanding clinical phenomena. Such efforts would be vastly facilitated by comprehensive reporting of whole-brain and region-of-interest results for all task conditions in experimental studies of clinical populations because this would allow the field to engage meta-analytic approaches more fully in our search for the pathophysiology of psychiatric disorders.

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