Risk for Mood Pathology: Neural and Psychological Markers of Abnormal Negative Information Processing

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Clinically, psychologists and psychiatrists have long known that depression is associated with altered processing of negative information, with depressed individuals frequently reporting an enhanced focus on negative (or potentially negative) information in their environment. Consistent with these clinical observations, a large body of empirical research has shown that depressed individuals show altered processing of negative stimuli[1] and consistent evidence for enhanced neural reactivity in brain regions thought to support the processing of salient emotional information, such as the amygdala.[2,3] However, the causal role of such abnormalities in information processing and amygdala activity has been a source of ongoing debate in the field. At the most simplistic level, researchers have been debating between 2 possible causal pathways. One potential pathway is that altered processing of negative information actually contributes to the development, maintenance, or recurrence of depression. If so, then one would expect to see such alterations in brain function and behavior to be present before the onset of clinical depression and to predict the likelihood of developing depression. However, an alternative pathway is the possibility that being in a depressed state leads individuals to more closely attend to or process potentially negative cues, leading to enhanced neural responses to such negative cues. If so, then one might expect such alterations to be present only when the individual is depressed. Arbitrating between these 2 possibilities is critically important, because evidence for the more causal pathway would lead researchers to increase their focus on behavioral and brain responses to negative information as potential targets for preventative interventions that might help alter the developmental trajectory of depression.

There have been hints in the literature to suggest that altered negative information processing and neural responsivity might play a causal role in the development of depression. For example, Joormann and Gotlib[4] found that previously depressed individuals continue to show a bias toward attending to negative faces, and that girls at risk for depression (but who have not yet experienced depression) show a similar bias.[5] Further, there is evidence that modifying the processing of negative information can help relieve depressive symptoms.[6] However, there has been relatively little evidence as to whether altered amygdala responsivity to negative stimuli is present in individuals at risk for depression, a finding that one would predict should be present if altered psychological and neural processing of emotional stimuli plays a role in the development of depression.

The recent elegant study by Pilhatsch *et al.*[7] provides evidence for the presence of such abnormalities in amygdala responsivity in adolescents at familial risk for clinical depression. Using a novel community-based sample of 164 typically developing 14-year-olds, Pilhatsch *et al.*[7] used functional magnetic resonance imaging to compare brain responses to negative versus scrambled pictures in 28 children with a family history of depression (high risk) and 136 children with no family history of depression (low risk). All children were screened for current or past probability of a psychiatric disorder and were excluded if a clinical interview confirmed the presence of such a disorder. They used a paradigm in which negative pictures could serve as the target (decide whether 2 negative pictures were the same or different) or as distractors (i.e., ignore the negative pictures and decide whether 2 scrambled pictures were the same). The logic of using this paradigm was to examine whether

enhanced amygdala reactivity occurred to negative pictures that were targets and distractors. If enhanced activity occurred in the 2 conditions, it would suggest a general alteration in the processing of negative stimuli. If it occurred only when participants should be ignoring the negative stimuli, it would suggest difficulty with the control or regulation of the processing of negative stimuli.[8]

Using region-of-interest and whole-brain analyses, Pilhatsch *et al*.[7] found that the high-risk adolescents showed increased left amygdala reactivity to negative faces, but only when the negative faces appeared as distractors, and not when they appeared as targets. Further, the whole-brain analyses showed similar patterns in a cluster including the right amygdala, hippocampus, parahippocampal gyrus, and right cerebellum. In addition, these researchers used psychophysiological interaction analyses to demonstrate that high-risk adolescents showed increased connectivity between the left amygdala and regions in the precuneus and postcentral gyrus/superior temporal gyrus during the processing of distractor negative pictures versus target negative pictures. The results are important because they demonstrate that adolescents at risk for depression show altered amygdala reactivity, but only when they should be ignoring such negative stimuli. This finding is consistent with prior work suggesting that the abnormalities in negative information processing in depression might reflect difficulties in emotion regulation and the ability to control attention to negative stimuli,[6] potentially combined with a stronger "bottom-up" response to such cues. However, there is also the possibility that the high-risk adolescents were able to appropriately ignore the negative distractors initially, but that their attention was recaptured by the negative stimuli after response selection. Future studies using techniques such as eye-tracking would help clarify the time course of attention to negative stimuli in high-risk individuals and thus further delineate the mechanisms that might contribute to altered negative information processing in relation to depression.

Pilhatsch *et al*.[7] were not the first researchers to study amygdala responsivity to negative stimuli in individuals at risk for depression, but their study did address some open questions generated from the results of prior functional imaging studies of emotion processing in familial risk populations. For example, Monk *et al*.[9] reported increased activity in the amygdala and nucleus accumbens to fearful faces and decreased nucleus accumbens activity to happy faces in the offspring of parents with a history of major depression. However, a large percentage of the high-risk offspring in this study had a history of an anxiety disorder, making it difficult to know whether the altered amygdala reactivity reflected risk for depression or a marker related to the past occurrence of anxiety. Given that Pilhatsch *et al*.[7] excluded individuals with a confirmed history of mood and anxiety disorders, their findings suggest that this altered amygdala reactivity is related to their high depression risk status. Mannie *et al*.[10] did not find altered amygdala reactivity to negative faces in young people with a parent with depression, although they did find decreased dorsolateral prefrontal cortex activity. However, Mannie *et al*. used a task in which the faces were the focus of attention and did not include a condition in which the negative stimuli needed to be ignored. Thus, Mannie *et al*. might not have found altered amygdala reactivity in high-risk individuals if it is more likely to occur when attention to negative stimuli needs to be regulated. Amico *et al*.[11] and Lisiecka *et al*.[12] compared adults with a family history of depression with adults with no family history of psychopathology and did not find differences in amygdala activity during 2 different paradigms involving negative stimuli. However, they excluded individuals with a personal history of an Axis I psychopathology, and the age of their samples was in the mid to late 30s. Thus, the individuals in their studies may have already passed through much of the risk period for depression onset, and they may have included resilient individuals unlikely to show altered emotional information processing.

In sum, the findings of Pilhatsch *et al*.[7] provide intriguing evidence that increased amygdala reactivity in conditions tapping emotion regulation is associated with risk for depression, consistent with the hypothesis that such abnormalities contribute to the development of depression. However, such findings are by no means a definitive indicator that altered neural and psychological processing of negative information plays a causal role in the emergence of depression. To provide stronger evidence, it will be important to pursue longitudinal follow-up work to determine whether the severity of alterations in negative information processing actually predicts the onset of clinical psychopathology and/or to determine whether prevention

efforts targeting remediation of such emotion regulation or attentional bias decrease the likelihood of developing depression. Further, it will be important to examine environmental factors that might moderate the development or expression of such alterations in negative information processing and brain activity, such as stress or trauma.[13,14] Another critical question is how early in development such alterations in the behavioral and neural indicators of altered emotional processing might emerge. There is evidence that altered amygdala reactivity is present even in very young children with clinical depression,[15] but it is not yet clear whether such alterations are also present very early in life in those at risk but who do not yet manifest clinical symptoms. Shedding light on the developmental trajectory of behavioral and neural indicators of risk will be critical for efforts to develop the most effective preventive efforts that ideally can be offered before the emergence of manifest psychopathology. &

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