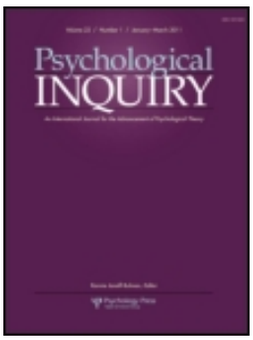

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Heterogeneity of Depression: Clinical Considerations and Psychophysiological Measures

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We are very sympathetic to Vaidyanathan, Vrieze, and Iacono's (this issue) call for studies integrating multiple methods and types of data to provide stronger tests of competing etiological hypotheses. In this commentary, we focus on the Depression section of the target article, because that is one of our major interests and we are concerned with many of the same questions as Vaidyanathan et al. We expand on some of the points raised in the target article, and in some cases provide a slightly different perspective. Specifically, we comment on several issues regarding the conceptualization and heterogeneity of the depression phenotype and consider the potential of affect-modulated startle and the error-related negativity (ERN), as well as several other event-related potential (ERP) markers, for addressing these concerns and contributing to understanding the etiology and pathophysiology of depression.

First, we applaud Vaidyanathan et al.'s argument that although depression may be a continuous construct, it is probably not unitary, and that it may be critical to parse the heterogeneity of depression using a temporal perspective (i.e., development and course). As they note, this is very consistent with some of our own views (e.g., Klein, 2008).

Vaidyanathan et al. emphasize the role of recurrent episodes in parsing the heterogeneity of depression. Indeed, the case for the validity of the single episode-recurrent distinction is strong: Recurrence has a number of important clinical correlates, such as greater comorbidity, higher rates of depression in first-degree relatives, history of early maltreatment, and more maladaptive personality traits/cognitive styles (Klein & Allmann, 2014). The single-recurrent episode distinction is also useful in treatment planning, in that there is a stronger case for maintenance treatment when patients have a history of recurrence.

However, as Monroe and Harkness (2011) argued, the assessment of recurrence is not as straightforward as it may seem. Many individuals with a single episode will subsequently have a recurrence. In addition, memory for past episodes is limited (Bromet et al., 1986), so some individuals with a history of previous episodes mistakenly report having a single episode. In addition, there are probably important differences among individuals with recurrent depressions—for example, those with two episodes spaced decades apart with full recovery in between, those with frequent but sharply demarcated episodes, and those with infrequent episodes spaced widely apart but still having residual symptoms or underlying dysthymia (*Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. [*DSM-5*]; American Psychiatric Association, 2013) in between. Similarly, there are likely important differences among individuals with a single episode—for example, those who with an acute onset and a short duration versus those with a long history of subthreshold symptoms or dysthymia before onset, or a single episode that persists for many years without full recovery (Klein & Allmann, 2014).

Recurrence is also correlated with two other important aspects of course: early onset and chronicity (Klein, 2008). Of importance, all three of these features have similar correlates, including histories of greater early adversity, more comorbidity, and greater familial liability (Klein & Allmann, 2014). Iacono's group has been among the few to try to parse age of onset from recurrence (Durbin & Hicks, 2014; Wilson, DiRago, & Iacono, 2014; Wilson, Vaidyanathan, et al., 2014). However, more work is needed to determine which of these features is most useful in parsing the heterogeneity of depression, and whether they can be combined to provide a life course perspective in delineating trajectories of depression over time (Klein, 2008; Klein & Allmann, 2014; Monroe & Harkness, 2011).

Returning to the issue of risky tests of causal hypotheses, Vaidyanathan et al. raise the critical, but surprisingly understudied, question of whether the liability to recurrence exists prior to the onset of depression or whether the factors influencing the onset of episodes changes over the course of the illness, perhaps due to the experience of the prior episodes themselves (e.g., kindling, stress generation). In a 14-year longitudinal study of a community sample of adolescents, Pettit, Hartley, Seeley, Lewinsohn, and Klein (2013) reported evidence supporting both models. Prior to first onset of major depressive disorder (MDD), subthreshold depression and parental history of recurrent depression distinguished individuals who went on to have recurrent episodes from those with a single episode. However, consistent with a stress generation model, after their first episode, individuals who later had a recurrence experienced a

greater number of life stressors than individuals who did not have another episode.

Vaidyanathan et al. propose that other types of data, for example, psychophysiological measures, may be useful in identifying subgroups of depression that may be associated with other clinical and course features, such as recurrence. In particular, they suggest that the affect-modulated startle response and ERN are inconsistent with a unidimensional view of depression and can be used to delineate more homogenous subgroups. We fully agree with this perspective, and we suggest additional neural variables that may be useful in parsing the heterogeneity of depression.

There is increasing focus on understanding psychopathology in terms of abnormalities of emotion; relevant to Vaidyanathan et al.'s article, emotion is a domain in which multiple measures and methodologies can be leveraged to test theoretical conceptions of psychopathology (Tracy, Klonsky, & Proudfit, 2014). Consider affective neuroscience studies of depression that utilize fMRI and focus on amgydala activation: MDD has been associated with both hyperactivation (Siegle, Steinhauer, Thase, Stenger, & Carter, 2002; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007) and hypoactivation (Ritchley, Dolcos, Eddington, Strauman, & Cabeza, 2011; Thomas et al., 2001) of the amygdala. The former data have been interpreted in terms of emotional hyperreactivity in MDD. Yet, consistent with the emotional context insensivity hypothesis of depression (Rottenberg, Gross, & Gotlib, 2005), many other physiological measures of emotional processing suggest that MDD is characterized by relatively *reduced* response to emotional stimuli (Bylsma, Morris, & Rottenberg, 2008).

As Vaidyanathan et al. note, in recent years bottom-up, empirically based models of the structure of psychopathology have provided considerable evidence suggesting significant overlap between depression and anxiety (e.g., Eaton et al., 2013). Moreover, this is largely mirrored by the structure of genetic influences (Kendler et al., 2011). However, there is also evidence of disorder-specific influences on these syndromes; indeed, ERN and affective modulation of the startle reflex distinguish depression and anxiety.

Both startle and ERN have been hypothesized to reflect activation of a defensive or threat system (Hajcak, 2012; Hajcak & Foti, 2008; Weinberg, Reisel, & Hajcak, 2012), and both are included as measures of threat constructs in the National Institute of Mental Health's Research Domains Criteria (Sanislow et al., 2010) negative valence systems domain. In addition to being theoretically related, the two measures are empirically correlated (Hajcak & Foti, 2008). As Vaidyanathan et al. indicate, anxiety disorders appear to be associated with a hyperactive ERN (also see Weinberg, Reisel, et al., 2012). However, studies of the ERN in depression have yielded very inconsistent findings.

Some of the inconsistency in this literature may be due to the failure to address comorbidity between depression and anxiety—few studies have simultaneously assessed anxiety in studies of depression, and vice versa. We have suggested that findings depend on the balance of anxiety and depressive symptoms. For example, Weinberg, Klein, and Hajcak (2012) found an increased ERN in "pure" GAD, but ERN in comorbid GAD/MDD did not differ from controls. We recently replicated this finding and examined a "pure" MDD group—which also did not differ from controls (Weinberg, Kotov, & Proudfit, 2015a). Moreover, across the entire sample, an *increased* ERN was predicted by self-reported checking symptoms, whereas a *decreased* ERN was predicted by self-reported symptoms of psychomotor retardation (Weinberg, Kotov, et al., 2015a). In a large sample of adolescents ($N = 550$), we again found that checking symptoms were associated with an increased ERN, whereas depressive symptoms were associated with a smaller ERN (Weinberg et al., in press). Thus, an increased ERN appears related to certain behavioral manifestations that cut across anxiety disorders (i.e., checking behaviors), whereas depressive symptoms relate to a smaller ERN.

In line with Vaidyanathan et al.'s suggestion that ERN may distinguish recurrent from nonrecurrent MDD, we recently found that maternal history of recurrent depression was associated with a reduced ERN in offspring (Meyer, Bress, Hajcak, & Gibb, under review). These findings were independent of children's current depressive symptoms, suggesting that a reduced ERN in children and adolescence may reflect exposure to, or risk for, more severe forms of depression.

Along similar lines, the ERN–anxiety link is not just a concomitant or consequence/scar—an increased ERN reflects vulnerability to anxiety. Two studies have found that unaffected first-degree relatives of OCD patients are characterized by an increased ERN (Carrasco et al., 2013; Riesel, Endrass, Kaufmann, & Kathmann, 2011); these data are consistent with the view that an increased ERN characterizes risk for psychopathology (Hajcak, 2012; Olvet & Hajcak, 2008; Proudfit, Inzlicht, & Mennin, 2013). Indeed, we recently found that a larger ERN in 6-year-old children predicts the subsequent first lifetime onset of anxiety disorders by age 9, over and above the effects of prior anxiety symptoms and maternal history of anxiety disorder (Meyer, Hajcak, Torpey-Newman, Kujawa, & Klein, 2015).

The startle response is another psychophysiological measure that has been linked with anxiety disorders in many studies (Vaidyanathan, Patrick, &

Cuthbert, 2009). In the target article, Vaidyanathan et al. (this issue) suggest that affect-modulated startle may also be blunted in more severe and recurrent cases of depression and that this may be a traitlike feature that could reflect vulnerability to certain forms of depression. However, it is unclear whether abnormalities in the startle reflex precede the first lifetime onset of depressive disorder or are a concomitant or consequence/scar of depressive episodes. We recently examined the affect-modulated startle response in the children of mothers with and without histories of depressive and anxiety disorders. Healthy offspring of mothers with a history of anxiety disorders exhibited increased startle responses following *both* negatively and positively valenced pictures (Kujawa et al., 2015). In contrast, there was no relationship between a maternal history of depression and children's startle responses. Thus, to the extent that an abnormal startle response is related to depression, it may be more a concomitant or consequence than part of a causal process. However, like the ERN, the startle response may reflect vulnerability to anxiety disorders.

Overall, then, as Vaidyanathan et al. argue, research on the startle response and ERN raise significant questions about the view of depression as a single, unidimensional set of psychopathological processes. Similarly, simple structural models that view depression and anxiety as largely the same form of psychopathology fail to map onto this growing body of literature. Instead, it appears that ERN and startle may be very useful in understanding the differences between these two closely intertwined forms of psychopathology and identifying more homogeneous subgroups within each disorder, as well as psychopathological features that cut across traditional diagnostic categories.

As Vaidyanathan et al. would certainly agree, there are other neural markers and processes may also prove valuable in parsing depression and understanding its etiopathology. For instance, we have examined the late positive potential (LPP), an electrocortical response that is larger following the presentation of emotional (i.e., both pleasant and unpleasant) compared to neutral stimuli (Cuthbert et al., 2000). We have argued that the LPP indexes sustained attentional engagement to emotional content (Ferri & Hajcak, 2015; Gable, Adams, & Proudfit, 2015; Weinberg, Ferri, & Hajcak, 2013). Moreover, in a twin sample, we recently reported substantial heritability in the magnitude of the LPP (Weinberg, Venables, Proudfit, & Patrick, 2015b), suggesting that the LPP may be a good candidate for a heritable biomarker of risk for emotional disorders. In line with the view that depression is characterized by reduced sensitivity to emotional content, we found a reduced LPP in response to threatening faces in adults with MDD (Foti, Olvet, Klein, & Hajcak, 2010). More recently, we replicated these findings using more complex and arousing visual stimuli—and found that the most pronounced reduction in LPP was evident among adults with early-onset MDD (Weinberg et al., in press). We have also found that among 550 female adolescents, the LPP was increased in relation to the personality dimension of extraversion and, in particular, in relation to the facet of positive emotionality (Speed et al., 2015)—a personality trait that Wilson, DiRago, et al. (2014) recently reported prospectively predicted the onset of MDD, but only for individuals who went on to experience recurrent episodes. We have also reported more direct links between the LPP and risk: We found that the LPP was reduced in response to emotional faces among 6-year-old children with maternal history of depression (Kujawa et al., 2011). In addition, we recently found that the LPP was blunted in response to both pleasant and unpleasant pictures in adolescent offspring of parents with a history of distress disorders (primarily depression, but also generalized anxiety and posttraumatic stress disorder), whereas it was elevated in response to unpleasant pictures among offspring of parents with fear disorders (primarily social and specific phobia; Nelson, Perlman, Hajcak, Klein, & Kotov, in press). Collectively, the data on the LPP suggest reduced attention to emotional content in current MDD, quite consistent with the emotional context insensivity view of depression. Moreover, a reduced LPP is particularly characteristic of early-onset depression, is evident in the offspring of mothers with a history of depression, and relates to emerging personality features linked to recurrent depression. However, a blunted LPP may be a traitlike feature that extends beyond depression to some anxiety disorders (the "distress" disorders), whereas it may be increased for other anxiety disorders (the "fear" disorders).

Another promising ERP marker of depression and risk is the Reward Positivity (RewP; Proudfit, 2014). The RewP derives from the electrocortical differentiation at frontocentral electrode sites approximately 300 ms following feedback indicating monetary reward versus loss. After losses, the ERP is characterized by an N2-like negative deflection previously referred to as the feedback negativity, or FN; following rewards, a relative positivity (the RewP) is observed (for a review, see Proudfit, Bress, Foti, Kujawa, & Klein, 2015). The RewP amplitude captures sensitivity to reward outcomes and is correlated with self-reported reward sensitivity and reward learning behavior. Source localization and combined ERP/fMRI indicate that RewP amplitude reflects activation of the basal ganglia (Foti, Carlson, Sauder, & Proudfit, 2014; Foti, Weinberg, Bernat, & Proudfit, 2015; Foti, Weinberg, Dien, & Hajcak, 2011).

Individuals with depressive diagnoses and symptoms exhibit a blunted RewP (Bress, Smith, Foti, Klein, & Hajcak, 2012; Foti & Hajcak, 2009; Liu

et al., 2014). Furthermore, the RewP is related to a family history of depression in healthy individuals (Foti, Hajcak, Kotov, & Klein, 2011; Kujawa, Proudfit, & Klein, 2014) and predicts increases in depressive symptoms (Bress, Meyer, & Proudfit, in press) and the onset of first lifetime major depressive episode prospectively (Bress, Foti, Kotov, Klein, & Hajcak, 2013). However, the RewP it is not associated with anxiety symptoms (Bress, Meyer, & Hajcak, 2015) or having a parent with a history of anxiety disorder (Kujawa et al., 2014). Moreover, the RewP may be useful in delineating a more severe and anhedonic/nonmood reactive subgroup of depression, as it is particularly blunted in offspring of parents with more severe depressive episodes (Kujawa et al., 2014) and in depressed individuals who exhibit anhedonia/lack of reactivity (Foti, Carlson, Sauder, & Proudfit, 2014; Liu et al., 2014).

As a final point, Vaidyanathan et al. suggest several designs, such as twin and adoption studies, as being particularly well suited to provide strong tests of causal hypotheses. We agree but would like to emphasize that many other designs can also be useful in testing etiological hypotheses, including sibling-pair studies, parent-offspring studies, and longitudinal studies focusing on putative etiological mechanisms. Moreover, although we strongly support the incorporation of multiple types of information that cut across units of analysis, we would not want readers to conclude that studies using self-report and interview data are no longer informative. Iacono and colleagues' work on the role of personality in the development and heterogeneity of depression provides an exemplary illustration of this (Durbin & Hicks, 2014; Wilson, DiRago, et al., 2014; Wilson, Vaidyanathan, et al., 2014). As another illustration, we recently found a striking nonlinear relationship between chronicity of depression and long-term symptom and functional outcomes that supports a qualitative distinction between chronic (or, following *DSM-5*, persistent) and nonchronic forms of depression (Klein & Kotov, submitted; for other evidence supporting this distinction see Klein, 2010). Although evidence of qualitative differences does not, in and of itself, indicate the nature of those differences, as Vaidyanathan et al. (this issue) note, providing more valid phenotypes will significantly advance the search for etiopathogenesis.

Note

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