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Depression and event-related potentials: emotional disengagement and reward insensitivity

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Event-related potentials (ERPs) provide economical neural indices of information-processing abnormalities in relation to depression and depression risk. Early ERP studies of depression focused on cognitive deficits, more recent studies have examined ERPs to emotionally and motivationally relevant stimuli. Both the late positive potential (LPP), a measure of sustained processing of motivationally salient stimuli, and the reward positivity (RewP), an index of reactivity to receipt of reward, appear to be diminished in individuals with major depressive disorder (MDD) and depressive symptoms, suggesting that depression is associated with emotional disengagement and deficits in reward processing.

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Overview

Event-related brain potentials (ERPs) are a cost–effective and direct measure of neural activity with excellent temporal resolution and are well-suited for understanding information processing abnormalities related to depression and risk for depression. We have examined ERPs among normative samples that vary in depressive symptom severity, individuals with diagnosed major depressive disorder (MDD), and children at high risk for depression based on maternal history of depression. In the current paper, we review recent ERP research on MDD and risk that focuses on deficits in emotion and motivation [1]. We emphasize ERPs elicited by emotional compared to neutral pictures, and the ERP differentiation between feedback indicating monetary gain and loss. By focusing on the processing of valenced stimuli, this review stands in contrast to previous work which has couched ERP abnormalities in MDD in terms of cognitive dysfunction [2]. The ERP work reviewed below suggests that MDD and risk for depression are characterized by deficits in emotional engagement and reward processing [3].

ERP abnormalities in MDD: from cognition to motivation

A wealth of data suggests that MDD is characterized by a *reduced* P300 [2]. In a typical P300 task, participants listen to frequent standard sounds, and must count or respond to relatively infrequent target sounds; the P300 is evident 300–500 ms following infrequent target stimuli as an increased positive potential at parietal sites. Bruder and colleagues report a mean effect size (i.e., Cohen's d) of .85 across many studies documenting a reduced P300 in MDD and link this abnormality to cognitive deficits in depression: the increased P300 to targets has been postulated to reflect cognitive processes that include memory and related constructs such as context updating [4].

An increased P300 has also been observed following the presentation of emotional compared to neutral stimuli [5–7]. When participants view both pleasant and unpleasant compared to neutral stimuli, the ERP is also characterized by a *sustained* positivity at midline parietal sites that has been referred to as the late positive potential [LPP; [8]]. We have argued that the P300 and LPP both reflect attentional engagement with salient environmental stimuli – and that salience can be determined by either task relevance (e.g., in an oddball task) or stimulus content [16]. We focus on the LPP in this paper; our view is that the reduced LPP in MDD may reflect deficits in attentional engagement with salient environmental stimuli, and might best be understood in terms of emotional and motivational abnormalities.

Very early studies using emotional words reported that individuals with MDD had a reduced LPP to both pleasant and unpleasant emotional words – but the LPP did not differ in response to neutral words [9]. Using pictures of dermatological disease, Kayser and colleagues [10] found that patients with MDD were characterized by a reduced LPP to unpleasant pictures.

These early studies are supported by a growing body of literature indicating that both clinical diagnoses of depression and depressive symptoms are associated with reduced LPPs to positive and negative emotional stimuli

in children and adults. For example, in a passive viewing paradigm, adults with MDD exhibited reduced LPPs to angry and fearful faces compared to healthy controls [11]. Relatedly, in clinical samples, depression predicted blunted LPPs to both unpleasant and pleasant emotional scenes (A MacNamara *et al.*, in preparation; A Weinberg *et al.*, in preparation). The effects of depression on the LPP appear to be most apparent for participants with an early onset depression (i.e., before age 18) or suicidality (A Weinberg *et al.*, in preparation). Little work has evaluated the LPP and depression across development; however, there is evidence of similar patterns in youth, with greater depressive symptoms associated with a reduced LPP to threatening faces in children and adolescents (A Kujawa *et al.*, under review).

Despite high comorbidity and shared etiological influences [12], depression and anxiety may be associated with distinct effects on the LPP. In one study, symptoms of generalized anxiety disorder (GAD) predicted an *increased* LPP to unpleasant images, but only when controlling for the blunting effect of depressive symptoms on the LPP (A MacNamara *et al.*, in preparation). Relatedly, youth with anxiety disorders exhibited *enhanced* LPPs to threatening emotional faces compared to controls, while greater depressive symptoms predicted *reduced* LPP to angry faces across both groups (A Kujawa *et al.*, under review). Lastly, in a very large sample of adolescents, reduced LPPs were related to low positive emotionality, a temperament trait thought to be specific to depression as opposed to anxiety [13], but negative emotionality, which characterizes both depression and anxiety, did not exhibit effects on the LPP (B Speed *et al.*, under review). Thus, decreased attention toward motivationally salient information, as measured by the LPP, may be relatively specific to depression, highlighting the importance of identifying core disturbances in emotional reactivity underlying psychopathology [1].

Lastly, reduced LPPs to positive and negative emotional faces and scenes have been observed among never-depressed offspring of parents with histories of depression, even in children as young as six years old [[14•]; Nelson B *et al.*, under review], suggesting that the LPP may be a vulnerability marker for depression. That is, reduced emotional reactivity is evident before the onset of depression in at-risk youth, and the LPP could be useful for identifying children most in need of prevention and early intervention.

Reward dysfunction in anhedonia

A defining feature of MDD is anhedonia, defined as markedly diminished interest or pleasure in normally enjoyable activities. In recent years, there has been growing interest in translating findings from basic neuroscience to characterize anhedonia in terms of dysfunction in reward-related brain circuitry, and in anhedonia as a potential endophenotype for MDD [15]. ERP research in this area has focused primarily on the electrocortical differentiation at frontocentral electrode sites that occurs 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 reward, a relative positivity (the reward positivity or RewP) is observed [16]. The RewP amplitude captures sensitivity to reward outcomes, and is correlated with indicators across other units of analysis, including self-reported reward sensitivity and reward learning behavior [17]. Source localization and combined ERP/fMRI indicate that RewP amplitude reflects – either directly or indirectly – activation of the basal ganglia by reward delivery [18–21].

Recent studies consistently demonstrate that RewP amplitude is a neurophysiological indicator of diminished reward sensitivity in MDD. In non-clinical samples, RewP amplitude is blunted among individuals with depressive symptomatology [22], an effect which is driven specifically by reduced neural activity to monetary gains [23•]. In clinical samples, RewP amplitude is blunted in patients with an MDD diagnosis compared to never-depressed controls [24•,25•]. These studies are consistent with fMRI findings of reduced activity in reward circuitry, including the dorsal/ventral striatum and orbitofrontal cortex [15]. Moreover, RewP amplitude is also associated with variability in reward functioning *within* MDD samples: In one study of patients with MDD, reduced RewP amplitude was associated with severity of self-reported anhedonia, even after adjusting for illness severity [24•]. In a separate clinical study, the effect of MDD diagnosis on RewP amplitude was found to be driven by a subgroup of patients who reported impaired mood reactivity to positive life events, a core feature of melancholic MDD – but not the full, *DSM*-defined melancholic subtype [25•]. These data suggest that reduced RewP amplitude may be a biomarker for an anhedonic/melancholic phenotype, accounting for heterogeneity within MDD populations that is not captured by the current diagnostic system.

Depression and ERPs elicited by gain and loss in childhood and adolescence

As in adults, depressive symptoms relate to reduced reward-related neural activity in children and adolescents. Among unselected 8–13-year-olds, those with greater depressive symptomatology show a blunted neural response to monetary losses compared to gains [26]; this association has been reproduced in the same sample at a two-year follow-up [27]. Notably, despite high comorbidity between depression and anxiety, the RewP appears to relate uniquely to depressive symptoms when controlling for the contribution of anxious symptoms [28].

The blunted RewP also relates to multiple measures of *risk* for depression. Low positive emotionality – a temperamental risk factor for depression [13,29] – at age 3 is associated with a reduced RewP at age 9 [30]. At age 9, children with a maternal history of depression – the best-established predictor of later depression in offspring [31–33] – show less neural differentiation between losses and gains than peers, even when controlling for the child's depressive symptoms [34,35]. This is particularly true if the mothers also exhibit low levels of positive parenting [35]. In addition to associations with established risk factors, the RewP has also been associated directly with subsequent depression in youth. A reduced RewP predicts subsequent depressive symptomatology in 8–13-year-olds [27] and subsequent first onset of major depressive episodes in 15–17-year-olds [36•] over the course of two years. Thus, accumulating evidence suggests that a blunted RewP may precede depressive symptomatology.

Several of these studies have examined depression in relation to the difference between gains and losses (i.e., ΔRewP); however, some studies have found that depression is specifically predicted by the RewP to monetary *gains*. In 8–13-year-olds, depressive symptoms relate both to the ΔRewP and to the RewP to gains, but not to the N2 to losses [26]. Likewise, RewP to gains, but not N2 to losses, measured at baseline in both 8–13-year-olds and 15–17-year-olds predict subsequent depressive symptomatology [27,36]. However, a contrasting effect has been found in 9-year-olds: maternal depression relates only to the ΔRewP, and not the RewP to gain or N2 to loss separately [35]. It will be important for future studies to examine both the RewP and N2, as well as the difference between them, in studies of depression and risk – especially across development.

Summary

ERPs provide economical neural indices of depression and depression-risk. Early ERP studies of depression focused on cognitive deficits, whereas more recent studies have examined ERPs to emotionally and motivationally relevant stimuli. Both the LPP, a measure of sustained processing of motivationally salient stimuli, and the RewP, an index of reactivity to receipt of reward, appear to be diminished in individuals with MDD and depressive symptoms, suggesting that depression is associated with emotional disengagement and deficits in reward processing. Compared to the effect size reported by Bruder and colleagues [4], the average effect size in our studies relating LPP to depressive symptoms and MDD diagnosis is somewhat smaller ($d = .60$); the association between RewP and depressive symptoms and MDD diagnosis is also moderate ($r = .33$ and $r = .40$ in adults and adolescents, respectively). One important area for future research may involve leveraging and combining multiple ERP measures (i.e., P300, LPP, and RewP) in the same studies of depression and risk – to examine potential combinations of biomarkers that may form biosignatures.

Interestingly, these findings are not observed in the anxiety disorders, despite their clinical and etiological overlap with depression. Moreover, among depressed individuals, blunted RewP is specifically associated with anhedonia and lack of mood reactivity, suggesting that it may be useful in parsing the heterogeneity of MDD. Finally, the offspring of parents with MDD exhibit diminished LPP and RewP, and blunted RewP in adolescents predicts subsequent increases in depressive symptoms and the first onset of MDD. Thus ERPs to emotional and motivational stimuli may also serve as vulnerability markers, and may be useful for identifying at-risk youth for prevention and early intervention. Important future directions will be to determine whether ERPs can be used to guide treatment selection in depression and if they are modifiable biomarkers that can also serve as treatment targets.

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