Commentary

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Doubling Down on Developing Reward System Neurobiology Markers of Antidepressant Treatment Response

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Reward system dysfunctions are increasingly conceptualized as transdiagnostic phenomena, relevant to many psychopathologies (1). The development of validated neural markers of reward processing that have utility for tracking clinical treatment response could, therefore, have broad mechanistic and clinical value in psychiatry, both for disorders in which reward-responsive circuits are overactive and for those in which they are underactive. In this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Webb *et al.* (2) take valuable preliminary steps in this direction; the study presents a thoughtful evaluation of electroencephalography (EEG)-based measures of reward processing as baseline measures predicting treatment outcomes and as measures of treatment-related change. More specifically, Webb *et al.* describe a psychotherapy treatment study of adolescent females with major depressive disorder who underwent EEG assessment of reward processing at 3 time points corresponding with pretreatment baseline, midtreatment, and the end of a 12-week course of cognitive behavioral therapy (CBT). A healthy comparison group, assessed with EEG at the same intervals, served as a valuable control of factors including time, repeat EEG assessment, and task exposure. However, there was no control available for the treatment manipulation. Two event-related potentials (ERPs) capturing early (the reward positivity [RewP]) and later (the late positive potential [LPP]) reward outcome processing were measured, as were frequency-based oscillations (theta and delta band total power during the RewP time window).

Key study findings regarding pretreatment baseline predictors were that larger baseline LPP to rewards and more delta power to losses was associated with greater symptom improvement, measured via Beck Depression Inventory II change score (importantly, multilevel statistical models were applied that accounted for LPP to losses and delta power to wins). In contrast to baseline prediction analyses in which pretreatment theta power was not related to treatment outcome, loss-related theta power was the only measure that suggested change with treatment. That is, multilevel model analysis revealed a group-by-time-by-condition interaction for theta power, such that the major depressive disorder group experienced a greater time 2 vs. time 1 reduction in theta power to losses (vs. wins) than the healthy control group, interpreted as a posttreatment normalization in major depressive disorder. These findings add to a small but growing literature evaluating reward-based EEG measures as biomarkers of antidepressant treatment. The Webb *et al.* study (2) is compelling along several dimensions, including identifying potential baseline predictors of CBT outcome (LPP, delta power) and possible mechanisms of CBT treatment response related to normalization of theta signaling during negative outcome processing. The study also points to several future research directions that are necessary for extending this work as part of larger efforts to ultimately validate reward-based EEG measures as clinical treatment response indices.

Reward processing is a broad construct comprising dissociable subcomponent processes (3). One major conceptual distinction parses reward-related functions into anticipatory "wanting" processes related to reward motivation and goal-oriented behaviors (largely dopaminergically mediated), relative to consummatory "liking" processes related to reward attainment (largely opioidergically mediated) (4). EEG can be used to parse in vivo brain activity during reward processing into constituent anticipatory and consummatory subprocesses with high temporal precision. EEG studies examining neural responses time-locked to reward outcome evaluation indicate a blunted RewP in depression (5,6). Although prior reward studies often focused on the RewP (3), interest is gaining in later components measuring downstream outcome processing, such as the LPP, thought to reflect motivational salience and affective processing, and to components preceding outcome that can be used to assess reward anticipation, such as the stimulus-preceding negativity and contingent negative variation, measured in the absence and presence of motor preparation, respectively (3). Webb *et al.* (2) focus solely on measures of reward outcome processing, an important phase in the time course of brain responses to reward. However, fully capitalizing on the temporal precision that EEG affords will require decomposing reward processing into subcomponent processes that include reward anticipation, consummation (reflected in feedback/outcome processing), and learning in order to examine their differential sensitivity as clinical treatment outcome measures. Further, research including passive and active tasks within the same study is also indicated in order to assess the impact of cognitive performance and motor responding on reward responsivity, a recognized confound that is rarely addressed in the clinical literature (7).

A notable strength of the Webb *et al.* study (2) is its combination of two types of EEG measures to evaluate CBT treatment response: time-domain ERPs (RewP and LPP) and frequency-domain neuro-oscillatory measures (theta and delta band power). Traditional time-domain ERP measures, by definition, collapse across all frequencies and only capture the phase-locked, evoked amplitude response. As a complement

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to the ERP approach, time-frequency analysis decomposes the EEG signal into more neurobiologically specific frequency bands. This information is of interest because distinct cognitive processes have been associated with different oscillatory activities. For example, neuro-oscillatory measures within the RewP time window have revealed frequency band disassociations relevant to reward processing with maximal delta and theta evoked power responses to wins and losses, respectively, providing convergent evidence that neural mechanisms underlying feedback processing differ by outcome. The potential clinical value of integrating ERP and time-frequency analysis in evaluating reward processing biomarkers is illustrated by a study combining measures of delta power with the RewP to enhance the sensitivity and positive predictive value of adolescent depression risk models (8). Expanding the measurement set further to include oscillation-based measures of neural synchronization (e.g., intertrial coherence) would be a useful extension of the findings of Webb *et al.* (2). Further, the authors should be commended for reporting EEG measure internal consistency and test-retest reliability, which can inform paradigm and variable selection for future trials. As the literature developing reward measures as treatment outcome variables grows, evaluating which EEG-based measures have the greatest sensitivity to treatment response will require vetting a comprehensive pool of candidate measures across reward subprocesses, task demands, and time- and frequency-domains. In addition to single measures, aggregated measures could yield composite variables or algorithms that may be of use in predicting treatment outcomes or indexing treatment-related change.

Notably, the RewP, which has garnered attention as a biomarker of depression (5,6), was not a baseline predictor of CBT treatment response, nor did it show significant treatment-related change. There is a well-developed empirical literature that substantiates depression-associated blunting of the RewP, putatively reflecting attenuated reward consummation. One possibility is that the Webb *et al.* study (2) lacked the power to detect RewP-related treatment effects. Additionally, there was no comparison for the manipulation of treatment (i.e., a patient group that received no treatment or a comparator treatment), so that the effects of CBT are uncontrolled. This limits inferences that can be made about the treatment under study. It will be valuable, as the authors readily acknowledge, to extend their prediction of CBT outcomes with EEG-based reward measures in well-powered studies with large-scale, multisite, randomized clinical trial (RCT) designs. Lastly, heterogeneity within depressive presentation may also play a role in the extent to which measures such as the RewP predict treatment outcome at the level of group means. Prior research demonstrates that underlying subtypologies (e.g., anxiety and melancholia) can have distinct reward processing signatures in depression (9,10). While the Webb *et al.* (2) study was not powered for subtype analysis, the moderate, albeit perisignificant, association (r = .44) observed between treatment reductions in loss-related theta power in the RewP time window and anxiety symptom reductions effectively highlights this point and warrants replication.

Of note, EEG-based measures offer several advantages as treatment response measures, including direct assay of brain functioning that resolves at the temporal resolution of neural activity (i.e., millisecond resolution). EEG is also relatively inexpensive to collect, store, and analyze, promoting the feasibility of scaling a predictive test for widespread clinical use. However, the poor spatial resolution and indeterminate source of scalp-recorded EEG are inherent limitations to the method. Multimodal studies that combine EEG techniques with those with better spatial resolution (e.g., functional magnetic resonance imaging, magnetoencephalography) will be needed for understanding the spatial covariation of EEG signals relevant to reward processing. Though integrative multimodal studies may be of less practical use for everyday clinical applications, they have critical value for increasing network-level understanding of potential EEG biomarkers.

Future progress also entails clearer separation of 1) studies designed to explore a wide field of candidate treatment predictor and change measures, validate their target engagement, and estimate effect sizes for clinical trial planning and powering from 2) studies involving the evaluation of treatment outcome in adequately powered RCTs designed to establish the evidence base for the clinical application of a biomarker. These processes, and their separation, represent a significant and exciting challenge to the mental health research field. Many potentially promising biomarkers have been identified but suffer from a lack of further development. Such later-stage development requires resource-intensive studies that are most likely to come out of multisite consortia efforts and/or public–private partnerships. If we are to one day realize the reward of validated biomarkers of authentic value in mental health practice, we need to double down by investing in and undertaking rigorous target engagement and biomarker validation and subsequently proceeding to well-powered RCTs that demonstrate the efficacy and define the use of such measures. Studies like those by Webb *et al.* (2) lay important groundwork in this ambitious endeavor.

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