Commentary

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Probing Psychiatric Symptoms with the Monetary Incentive Delay Task

Brian Knutson and Andreas Heinz

The promise of neurophenotyping psychiatric symptoms implies a need for methods that yield reliable and valid measures of brain activity in individual patients. Balodis and Potenza (1) have provided a comprehensive and nuanced review of the use of the monetary incentive delay (MID) task to probe symptoms related to addiction. In this commentary, we briefly reflect on the history of the MID task, situate these findings within the broader context of other disorders, and speculate about implications for research and practice.

The first author (BK) developed the MID task during the latter half of the 1990s as a postdoctoral fellow in Hommer's intramural laboratory at the National Institute on Alcohol Abuse and Alcoholism. Inspired by success of researchers using functional magnetic resonance imaging to map neural correlates of sensory and motor function, the MID task was designed to leverage the spatial and temporal resolution of functional magnetic resonance imaging (i.e., millimeters and seconds) to "localize" affective responses deep in the brain.

Because individuals varied in their affective responses to other incentives (e.g., images, sounds, tastes), money was adopted as an incentive that could influence affect more consistently. Money also provided a convenient experimental stimulus because it could be 1) either gained or lost (i.e., assigned positive or negative valence), 2) cued as well as delivered (i.e., distinguishing responses to anticipation vs. outcomes), and 3) cued with different attributes (e.g., signifying valence, magnitude, probability, uncertainty, delay, effort). Incorporating both gain and loss conditions allowed researchers to control for potential confounds related to sensory stimulation, arousal, salience, and motor preparation. Researchers could also stabilize dynamic expectations within subjects after brief training (including learning) and control performance across subjects with adaptively timed targets, facilitating assessment of reliable affective and neural responses to incentives (2).

Initial findings indicated that experientially, MID task gain cues elicited "positive aroused" affect, whereas loss cues elicited "negative aroused" affect—suggesting that incentive anticipation and outcomes could powerfully induce affect. Neurally, gain cues proportionally increased activity in the nucleus accumbens (NAcc) of the ventral striatum, whereas both loss and gain cues proportionally increased activity in the anterior insula and medial caudate. Even within cues, individual differences in NAcc activity correlated with positive arousal. The MID task became a popular "localizer" for eliciting NAcc activity during reward anticipation (2). activity of the NAcc during anticipation of large gains (e.g., +$5.00) versus nongains (e.g., +$0.00) typically shows large effect sizes (e.g., $f^2 = 3.07$), implying that significant results can be obtained in small samples (e.g., six subjects at a power of .80) (3).

Beyond inducing affective states, the MID task has also been used to probe affective traits, which may relate to psychiatric symptoms (4). However, individual difference measures must first demonstrate reliability (or stability of measurement) before their validity (or distinct associations with predicted traits) can be verified. Test-retest assessment of neural activity elicited by the MID task ($n = 14$, interval >2.5 years) revealed significant temporal stability but only in large incentive conditions (i.e., intraclass correlations >.50 for left NAcc activity during anticipation of large gains and right anterior insula activity during anticipation of large losses). Only these reliable neural markers showed significant and valid associations with affective traits ($n = 52$), such that left NAcc activity during anticipation of large gains correlated with a positive aroused trait (i.e., related to extraversion, positive affect, and behavioral activation), whereas right anterior insula activity during anticipation of large losses instead correlated with a negative aroused trait (i.e., related to neuroticism, negative affect, and behavioral inhibition). These findings suggest that peak activity measures within MID task conditions may have higher reliability than contrasts across conditions and so provide more valid markers of trait affect (3).

Beyond positive aroused traits, increased NAcc activity during reward anticipation has also been associated with lower impulsivity in samples with a diagnosis of addiction (1) and in samples with a diagnosis of attention-deficit/hyperactivity disorder (5). Although the combination of high positive arousal and low impulsivity may seem paradoxical, these traits may share a complex relationship, particularly in extreme cases. Highly impulsive individuals may chronically experience diminished positive arousal (i.e., more boredom and less excitement). These combined traits warrant further investigation because impulsivity confers risk for developing addiction and other psychiatric disorders (6).

The second author (AH) collaborated with the first author during a research fellowship in Weinberger's intramural laboratory at the National Institute of Mental Health. He began to use the MID task to explore incentive processing in different psychiatric patient groups after returning to Germany to lead the Psychiatry Department at Charité Hospital. By applying the same task across different disorders, a picture began to emerge of which psychiatric symptoms consistently aligned with blunted neural activity during reward anticipation.

Schizophrenia and unipolar depression (or "neurosis") represent two of the earliest psychiatric diagnoses. In schizophrenia, initial findings using the MID task in drug-free patients who experienced a first episode of schizophrenia revealed blunted ventral striatal activity during reward anticipation, and this blunting correlated with self-reported "negative" (or low positive arousal) symptoms. The same patterns were obtained

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in patients treated with typical antipsychotics (thought to block dopamine receptors) but not in patients treated with atypical antipsychotics (thought to target other neurotransmitter systems) (7). In unipolar depression, however, findings using the MID task have not shown blunted ventral striatal activity as consistently during reward anticipation, with evidence instead tending to implicate diminished neural responses to reward outcomes (8).

Application of the same task across different disorders allows investigators to determine not only effect significance but also effect size. In an informal survey of MID task findings, we compared ventral striatal activity during reward anticipation in samples of patients with schizophrenia versus unipolar depression (available on request from BK). Across studies, patients with schizophrenia showed considerable blunting of ventral striatal activity (average $r = .54$, $n = 8$ studies), but patients with unipolar depression did not (average $r = .12$; $n - 3$ studies). Negative symptoms in patients with schizophrenia correlated with blunted ventral striatal activity during reward anticipation (average $r = -.64$; $n = 6$ studies). Together, these results imply that blunted ventral striatal activity during reward anticipation provides a neurophenotypic marker of negative symptoms in patients with schizophrenia, but further verification is required in patients with unipolar depression.

Even after controlling for diagnosis, neurophenotypic markers can still be linked to psychiatric symptoms. In a direct comparison of different patient groups, patients with schizophrenia (to a greater extent) and patients with unipolar depression (to a lesser extent) showed blunted ventral striatal activity during reward anticipation relative to healthy control subjects (9). Controlling for disorder, depressive symptoms (assessed with the Beck Depression Inventory), but not anxious symptoms (assessed with the State–Trait Anxiety Inventory), correlated with blunted ventral striatal activity during reward anticipation. Although high negative arousal versus low positive arousal items were not distinguished in depressive symptoms (10), the absence of an association with anxiety implicates low positive arousal. With respect to addiction, an alcohol-dependent group also showed this blunting, and all analyses controlled for potential demographic confounders (e.g., sex, age, smoking).

After surveying a growing literature, the fact that neural responses to monetary incentives are linked to psychiatric symptoms still seems remarkable. Currently, the MID task reliably evokes affect, and affective traits lie at the core of prominent psychiatric symptoms. At the present time, the MID task appears to provide a neurophenotypic probe of negative symptoms in schizophrenia. Although evidence for blunted ventral striatal activity during reward anticipation in addictive disorders is more mixed, after accounting for sources of diagnostic variance (e.g., drugs on board, comorbidity, addiction stage), the MID task (combined with other cue tasks) may eventually yield neural markers of addiction (1).

A decade of using the MID task to probe psychiatric symptoms has taught us much, including 1) reliable neural measures have a better chance of showing validity, 2) individual symptom profiles may provide finer resolution than group diagnoses, and 3) effect sizes rather than mere significance may improve diagnostic specificity. Additional practices that could accelerate progress include 1) using adequate resolution to detect fast changes in subcortical activity, 2) applying comparable paradigms across disorders, 3) reporting conditional in addition to contrast data (e.g., within subjects and across groups), and 4) reporting whole-brain results in addition to volume of interest results.

Research on neurophenotypic probes continues to hold great promise, including physiological studies that illuminate underlying neural contributions to neuroimaging signals (e.g., dopaminergic contributions to NAcc activity on functional magnetic resonance imaging), longitudinal studies that use probes to disentangle psychiatric cause from consequence (e.g., whether affective traits confer vulnerability to addiction or the reverse), and clinical studies that use probes to predict outcomes and guide therapeutic treatment.

In conclusion, neurophenotyping requires reliable and valid neural measures that align with psychiatric symptoms. The psychotherapist Abraham Maslow famously cautioned "… it is tempting, if the only tool you have is a hammer, to treat everything as if it were a nail." (11) At the present time, the MID task holds promise as an index of some psychiatric symptoms —until a better tool comes along. In the meantime, we will work toward and welcome that day.

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