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SPECIAL ISSUE/PRECLINICAL ASSAYS

Towards translational biomarkers for motivation: A commentary on Noback et al. (2024)

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Motivational deficits are a defining feature of psychiatric disorders, such as depression and schizophrenia. However, translational researchers have struggled to make significant advancements in reproducible biomarkers that may hint at their underlying mechanisms. In particular, progress has been stalled by a paucity of studies that seek to test the same biomarker across species. The utility of cross-specifies biomarkers lies is their ability to facilitate invasive, mechanistic preclinical studies of biomarker signals that can be readily measured in human populations.

In their recent article, Noback et al. (2024) address this gap through their use of a progressive ratio breakpoint task (PBRT) across species to better understand the mechanisms that underly motivational deficits. Traditionally, the PRBT has been used to measure motivation in the form of actions (e.g., button presses, nose pokes) that are performed repeatedly over a given period. The highest number of actions that a subject is willing to perform is referred to as their "breakpoint." The breakpoint has been used across species to examine motivation for drugs and natural rewards in experimental animals and humans. It also has been used to examine motivational deficits in psychiatric disorders, such as depression and schizophrenia. Prior to this paper, members of this same research team provided evidence for a PRBT electroencephalographic (EEG) biomarker of elevated alpha band power over the parietal cortex that consistently preceded hitting the breakpoint in mice and humans (Cavanagh et al., 2021). Moreover, in humans, the strength of this increase was correlated with overall effort.

Noback and colleagues sought to probe the underlying neurochemistry of this biomarker using an amphetamine challenge paradigm. Specifically, they tested whether amphetamine would increase willingness to work on the PRBT and whether this behavioral change would be reflected in parietal alpha power. Consistent with previous findings, amphetamine increased the breakpoint in humans. In mice, amphetamine increased the breakpoint at 0.3 mg/kg when they were not tethered to EEG equipment. In contrast, amphetamine unexpectedly *decreased* the breakpoint in mice at 1 mg/kg when they were tethered to EEG equipment. Although previous research, and their second mouse cohort, has shown that amphetamine increases motivation, previous studies in rats also have shown that amphetamine can exert dose-dependent biphasic effect on motivation such that lower doses (0.25 mg/kg) can increase motivation, whereas higher doses (0.5 mg/kg) can decrease motivation (Floresco et al., 2008). The biphasic effect of amphetamine has been attributed to its ability to suppress appetite and by extension, desire for food rewards. In other words, it has been speculated that at higher doses, amphetamine may suppress appetite so much so that nonhuman animals are less motivated to work for food rewards.

While the behavioral effects of amphetamine were relatively consistent with previous literature, the effects on the EEG biomarker were less clear. At baseline (vehicle or placebo), the authors replicated their previous findings in mice and humans by showing that alpha power increased in both species as they reached their breakpoint. However, there was no evidence that amphetamine significantly altered parietal alpha power for either mice or humans. The authors of the study concluded that their findings support the pharmacologic predictive validity of the PRBT across species, but that the utility of parietal alpha power as a biomarker of motivation as assessed by the PRBT was uncertain.

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Overall, Noback and colleagues should be applauded for their use of cross-species paradigms to investigate translational behaviors and biomarkers. Such investigations are critical for strengthening translational research, and hastening its impact on diagnosis and treatment. However, their findings raise questions as to whether the EEG biomarker is truly tracking motivation or some other cognitive process that occurs close to the breakpoint. The fact that amphetamine seemed to de-couple effortful behavior from parietal alpha power begs the question, if the EEG biomarker is not tracking effort, what is it tracking? Elevated alpha power has been observed during active and not passive listening (Dimitrijevic et al., 2017). Therefore, the elevated alpha power observed prior to reaching the breakpoint could reflect the increased cognitive resources required to sustain attention near the breakpoint. It is also possible that the EEG biomarker tracks cognitive workload. A recent meta-analysis suggested that there is an inverse relationship between alpha power and cognitive workload (Chikhi et al., 2022). Because alpha power increases right before a participant's breakpoint, this biomarker could reflect a decreased need for cognitive resources to complete a task due to the decision to discontinue it. Future studies might test this theory by exploring whether there is evidence of elevated alpha power on tasks in general when they are discontinued. In either case, it will be exciting to see the how this line of research helps the field identify trans-species biomarkers for motivational states.

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