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EDITORIAL

Cardiac rhythms as windows into brain stimulation response: Promise and pitfalls in precision psychiatry

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The challenge of depression

Depression remains one of the most pressing challenges in psychiatry, with a heterogeneous presentation and incomplete response to current treatments. In recent years, an increasing body of work has pointed to multiple disturbances as modulators of depressive phenotypes. Within this evolving framework, in this issue of *Brain Medicine*, Goya-Maldonado and colleagues made novel contributions that highlight the roles of distinct systems (1). By situating depressive disorders within a systems-level context, their work exemplifies how mechanistic insights can inform the search for novel, biologically grounded treatment strategies.

Study design and core questions

Their study tackles two critical questions in contemporary neuromodulation research. First, can functional connectivity guide optimal stimulation site selection? Second, do immediate physiological responses predict long-term clinical outcomes? The investigators enrolled 75 patients with major depressive disorder in a quadruple-blind crossover trial, comparing personalized stimulation sites based on individual resting-state connectivity with standard F3 positioning. Throughout stimulation sessions, continuous electrocardiogram monitoring captured heart rate dynamics, with a focus on beat-to-beat deceleration and heart rate variability measures.

The results paint a nuanced picture of treatment prediction. Patients who showed greater heart rate deceleration within the first 45 seconds of initial stimulation demonstrated superior clinical improvement at the six-week follow-up. This relationship held specifically for active stimulation, suggesting that immediate autonomic responses reflect meaningful target engagement rather than nonspecific effects. The correlation between early cardiac modulation and eventual symptom reduction offers tantalizing evidence that the frontal-vagal pathway serves as a real-time indicator of therapeutic neural circuit activation (1).

Promising biomarker: Heart rate deceleration

This finding builds on emerging evidence linking prefrontal stimulation to downstream autonomic effects through subcortical relay stations. The proposed mechanism involves signal propagation from the dorsolateral prefrontal cortex through the subgenual anterior cingulate cortex to brainstem nuclei controlling vagal tone (see Figure 1) (2). When iTBS successfully engages this network, the resulting cardiac deceleration may signal effective neuromodulation of mood-regulatory circuits. Previous work in healthy volunteers has demonstrated that F3 stimulation optimally induces such heart rate changes (3), and preliminary studies in depression have shown trends toward associations between cardiac modulation and clinical response (4).

The implications extend beyond simple prediction. If validated, cardiac biomarkers could enable real-time optimization during treatment sessions. Clinicians can adjust coil positioning, stimulation intensity, or other parameters based on immediate physiological feedback, potentially improving response rates, which currently hover around 30-50% for standard protocols (5). This approach sidesteps the limitations of motor threshold determination, which relies on anatomical assumptions that may not translate to prefrontal targets. Instead, cardiac monitoring provides direct evidence of relevant circuit engagement.

Unexpected complexity in heart rate variability

However, the study by Wilkening et al. reveals unexpected complexity in heart rate variability responses (1). While the root mean square of successive differences (RMSSD) increased during active stimulation compared to sham, higher increases paradoxically predicted poorer outcomes at one-week assessment. That was unexpected! This counterintuitive finding challenges prevailing assumptions about autonomic flexibility in depression. It is particularly striking, as it highlights the significant gaps in our understanding of the temporal dynamics of brain–heart interactions during neuromodulation. The authors suggest that effective frontal-vagal engagement may initially reduce variability during stimulation, followed by compensatory increases that align with clinical improvement. However, this explanation remains speculative, highlighting gaps in understanding the temporal dynamics of brain-heart interactions during neuromodulation.

The personalized targeting paradox

Equally unexpected is the failure of personalized connectivity-based targeting to outperform standard F3 positioning. Despite sophisticated neuroimaging protocols identifying individual sites with maximal anticorrelation between the left dorsolateral prefrontal cortex and the default mode network, personalized stimulation yielded no clinical advantage (1). This null finding contradicts influential studies suggesting that connectivity-guided targeting improves outcomes (6, 7).

Technical limitations warrant consideration. Despite neuronavigation, the actual stimulation sites deviated from ideal targets by more than 10 millimeters in some participants from the personalized group. Those discrepancies, while reflecting real-world implementation challenges, could dilute the potential benefits of individualized targeting.

The discrepancy nonetheless raises fundamental questions about the reliability and generalizability of imaging connectivity biomarkers for depression treatment using TMS. That said, the need for precision targeting is increasingly recognized as a necessary component for optimal response to other neuromodulation treatments, notably deep brain stimulation (8) and focused ultrasound (9). Beyond the precise delivery of the intended treatment, the state of the targeted network itself may be a contributing factor that impacts both biomarker behavior and response trajectories (10).

Methodological considerations

The crossover design, while strengthening internal validity, introduces interpretive complexities. A parallel-group comparison might have clarified whether personalized targeting benefits emerge at specific therapeutic windows. The authors acknowledge this limitation, noting that averaging

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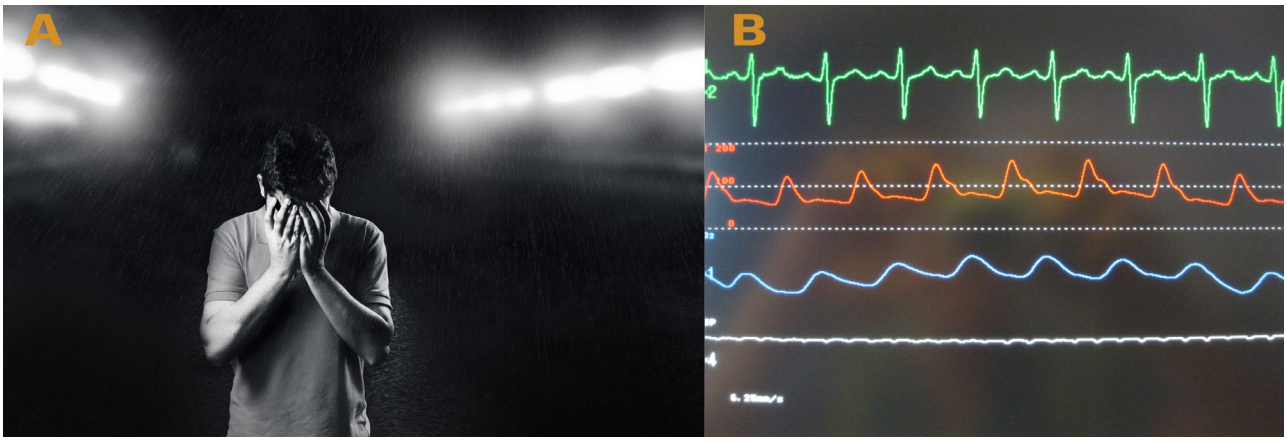

Figure 1. Depression and cardiac biomarkers in brain stimulation therapy. (A) Depression affects millions worldwide, with at least one-third of patients not responding well to conventional treatments. (B) Electrocardiogram patterns during brain stimulation showing heart rate deceleration within 45 seconds (increased intervals between beats) that predicts treatment success at 6 weeks. Image sources: (A) Fotorech, Pixabay, 2015; (B) John Campbell, Flickr, 2016. Both CC0 via Wikimedia Commons.

across intervals provides conservative estimates but may obscure temporal patterns of response (1).

Future studies employing parallel-group designs with consistent follow-up periods could clarify whether personalized targeting (or accelerated protocols) benefits emerge at specific therapeutic windows.

Methodological considerations also extend to the cardiac measurement approach. The study assessed RMSSD during stimulation rather than at rest, capturing stimulation-induced entrainment rather than baseline autonomic tone. This difference matters because iTBS likely induces transient heart-brain coupling that differs mechanistically from tonic vagal activity (11). Other mechanisms have also been posited using changes in heart rate evoked potentials over the course of subcallosal cingulate region deep brain stimulation (12). While Wilkening and colleagues appropriately acknowledge this nuance, the field lacks consensus on optimal cardiac assessment protocols during neuromodulation.

Moving forward, standardization of measurement approaches will prove essential for cross-study comparisons and clinical translation. That said, the focus on new metrics that can index critical interoceptive features at the core of major depression is an important advance.

Symptom-specific biomarker limitations

The selective association with Montgomery-Åsberg Depression Rating Scale (MADRS) scores, but not with the Hamilton Depression Rating Scale (HAMD) or Beck Depression Inventory (BDI), highlights another challenge (1). Different scales emphasize distinct symptom domains, with the MADRS loading heavily on observed mood, the HAMD on neurovegetative features, and the BDI on cognitive symptoms (see Table 1) (13). The finding that cardiac biomarkers predict mood changes but not other symptom clusters suggests a specific underlying mechanism that warrants further investigation. Future research should examine whether different biomarkers predict improvements in specific symptom dimensions, potentially enabling more targeted treatment selection (14).

Several additional factors might explain this negative result. The heterogeneity of depression likely obscures group-level effects, with different symptom profiles responding to specific stimulation targets (15). An alternative consideration is that brain state, rather than symptoms, may more reliably stratify patients into the treatment option most likely to be effective, while also avoiding those that will not (16). Brain state signatures that guide treatment selection at all stages of illness, as well as identify markers of illness progression, are a critical need, particularly with the increasing availability of new treatment options for increasingly difficult-to-treat patients (17).

Challenges in precision psychiatry translation

The findings also underscore broader challenges in precision psychiatry. It remains a failure of research translation that, despite decades of biomarker research and several putative treatment selection biomarkers, clinical practice still relies heavily on trial-and-error prescribing. The field continues searching for the psychiatric equivalent of HER2 testing in breast cancer or EGFR mutations in lung cancer, biomarkers that fundamentally alter treatment decisions. Cardiac monitoring during iTBS represents progress toward this goal; however, substantial implementation hurdles remain. Equipment costs, training requirements, and workflow integration pose practical barriers even if the science proves robust.

Future research directions

As we look forward, several research priorities emerge. Replication in larger, more diverse samples will establish generalizability across demographic and clinical populations. Head-to-head comparisons of different biomarker approaches: cardiac, electroencephalographic, and neuroimaging, could identify optimal prediction strategies or complementary marker combinations. Mechanistic studies using concurrent neurophysiological recordings might clarify how cardiac responses relate to neural

Table 1. Depression rating scales and their primary symptom domains

Scale	Primary Focus	Key Domains	Cardiac Biomarker Association
MADRS	Observed mood	Clinical observation of mood symptoms	**Significant correlation** with HR deceleration and clinical improvement
HAMD	Neurovegetative features	Sleep, appetite, physical symptoms	No significant association
BDI-II	Cognitive symptoms	Thought patterns, self-perception	No significant association

MADRS = Montgomery-Åsberg Depression Rating Scale; HAMD = Hamilton Depression Rating Scale; BDI-II = Beck Depression Inventory-II; HR = heart rate.

circuit dynamics. Clinical trials directly comparing biomarker-guided treatment protocols with standard treatment protocols will ultimately determine whether physiological monitoring improves patient outcomes.

Reconsidering depression neurobiology

The work also raises philosophical questions about psychiatric nosology and treatment targets. If cardiac responses predict improvement better than sophisticated neuroimaging, what does this imply about depression neurobiology? Peripheral physiological markers capture integrative processes that focal brain measures miss. Alternatively, the focus on prefrontal-subcallosal cingulate connectivity might be replaced by more autonomic- or interoceptive-specific functional connectivity pathways (18). Alternatively, cardiac monitoring may provide more reliable and less noisy signals than current neuroimaging approaches. Resolving these possibilities requires continued integration of central and peripheral measurement strategies.

Conclusions: Practical over sophisticated

The study by Wilkening, Jungeblut, Goya-Maldonado, and colleagues advances the field by demonstrating that readily obtainable physiological measures predict brain stimulation outcomes (1). Their rigorous methodology and transparent reporting of both positive and negative findings exemplify good scientific practice. While personalized targeting based on connectivity may be disappointing, cardiac biomarkers offer a new and practical path toward treatment optimization. As the field continues to pursue precision psychiatry, this work reminds us that the most sophisticated approach may not always prove the most effective. Sometimes, listening to the heart provides more explicit guidance than mapping the brain.

Taken together, the work of Goya-Maldonado and his team underscores the importance of looking at depression not merely as a set of symptoms, but as a complex condition shaped by multiple systems. This integrative perspective moves the field away from narrow categorical models and toward a biologically informed framework that is both mechanistic and clinically relevant. By framing depression through a systems-level lens, his team's contributions challenge us to move beyond symptom clusters toward mechanistically guided therapies, a direction that may redefine the field in the years ahead.

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