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NEWS AND COMMENTARY

Personalized treatments for psychiatric disorders and flexible assessment of neural function

Rethinking strategies for when to acquire neural markers associated with treatment response

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By uncovering a more mechanistic understanding of the pathophysiology of psychiatric illness, neuroscience research can advance psychiatry toward personalized treatment. In this ideal world, treatment decisions—whether psychological or pharmacological—are guided on biological factors of individual variation. Achieving these goals requires neuroscientists to embrace individual differences to link changes in neurobiology to the course of clinical response. Ideally, achievement of such personalized approaches to treatment would entail continuous measurement of a variety of psychological and biological factors to identify who is going to improve in response to which treatments and in what time frame. Although this is a challenging task, one study design described here has yet to be utilized and may bring us closer toward personalized treatment.

Put simply, this design would flexibly acquire neurobiological measures at the intervals when patients maximally improve or decompensate. This approach diverges from current approaches that assess all patients at prescribed intervals (for example, every 8 weeks). This method carries mobile device-based assessments of symptom severity using ecological momentary assessment (EMA) in conjunction with functional imaging and identifies the neural mechanisms contemporaneously associated with symptom change.

The rationale for imaging patients when they evidence the largest changes in functioning arises from the typical course of symptom amelioration during treatment.[1] In psychotherapy[2] and pharmacotherapy[3] outcome studies of mood and anxiety disorders, most patients do not respond linearly. The modal pattern of treatment response is stepwise and discontinuous. Discontinuous changes in symptom severity are called 'sudden gains.' Individuals evidencing sudden gains tend to have a better prognosis.[4] Conversely, many individuals receiving treatment for depression and post-traumatic stress disorder show evidence of short-lived increases ('spikes') in symptom severity,[5] before an overall pattern of symptom reduction.[6] However, the precise timing of discontinuous changes in symptom severity differs across patients. Thus, functional magnetic resonance imaging (fMRI) treatment studies that scan at prescribed intervals often cannot capture the acute changes in neurobiology when symptoms change the most.

This type of design requires frequent assessment of patient symptom severity to uncover critical periods of symptom change for each patient. With such temporal resolution of symptom severity, neurobiological data (for example, a fMRI scan) can be acquired from the patient at the critical juncture when sudden gains occur. The use of EMA—cell phone-based assessment of psychiatric symptoms—makes it possible to identify when discontinuous symptom shifts occur. Frequent EMA of psychiatric functioning is feasible (response rates often between 70–80%), reliable (intraclass correlation >0.88) and sensitive to shifts in symptom severity.[7] Further, using item response theory (IRT) to assess psychiatric symptoms using EMA[8] makes this approach more feasible by reducing patient response burden such that patients need only complete 3–5 items for a valid assessment of severity. IRT approaches are also more sensitive than classical assessments by only assessing symptom severity within narrower windows of the patient's current functioning. Other objective EMA approaches may also determine changes in functioning and trigger scheduling of an fMRI scan. As one example, geolocation movement data may indicate when a depressed patient is behaviorally activated and improving, or when a bipolar patient is entering a manic phase. Together, these approaches can facilitate identification of changes in patient functioning and trigger imaging shortly thereafter.

Evidence supports the feasibility, reliability and sensitivity of fMRI (particularly, resting-state fMRI (rs-fMRI)) for such a design. One rs-fMRI study that scanned an individual three times per week for 18 months found high reliability/stability of rs-fMRI networks (dice coefficient = 0.87).[9] Similarly, several labs have demonstrated longitudinal neural network changes resulting from psychiatric treatment,[10] suggesting that fMRI is sensitive to treatment-related changes in symptom severity. From a feasibility standpoint, the ability to schedule and scan a patient within 24 h of a sudden gain is difficult, but doable. Particularly, if relatively short (~10–15 min) rs-fMRI scans are acquired, fMRI sessions could be completed in as little as 30 min.

It will be paramount to determine the amount of change in symptom severity required to trigger a scan. Previously, sudden gains in depression have been defined as Beck Depression Inventory reductions of >7 points or 25%.[4] However, a more idiographic approach is to estimate mean and variability of symptom severity for each patient before the treatment. EMA acquisition of symptom severity 1–2 weeks before treatment yields baseline data indicating how much change in severity is required to trigger imaging. This individualized approach would suggest that patients with stable severity require less change to trigger fMRI assessment, whereas patients with more variable severity require more substantial change in symptoms for imaging. Patients who do not respond to treatment would be scanned after a predetermined number of weeks. Such a patient-centered approach accounts for differences at both the illness (for example, anxiety vs depression) and patient levels.[1]

Identifying those neural circuits proximally associated with sudden gains may be particularly useful to facilitating treatment.

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Such data could be used to determine which neural circuits should be targeted by deep brain stimulation or in novel drug development. Similarly, prior to major shifts in psychiatric functioning, subtle changes in specific neural circuits may indicate that a change in treatment is needed or the likelihood that the patient will drop out. These types of data could speak of the probability of such an event occurring. Furthermore, individualized approach to treatment permits clinical neuroscientists to determine whether changes in certain neural circuits resulting from treatment are state effects (reflecting acute neural alterations associated with symptom change), or are compensatory processes that emerge in the days and weeks after functional improvements. Finally, in addition to revealing the proximal neurobiological changes associated with acute changes in symptom severity, this approach may enhance clinical care: data from these designs could be used to notify providers when shifts in symptom severity are occurring to facilitate changes in treatment on the fly instead of waiting until the following visit.

Current designs examining associations between neural markers and treatment outcome have relied on designs in which patients are assessed at regular and prescribed intervals. This approach has yielded substantial power to examine primarily group differences pertaining to neural mechanisms associated with the treatment response. Given the inevitable discontinuity between the changes in symptoms and the timing of neural assessment, a limitation of this approach is in determining whether changes in neural circuits are in fact acute neurobiological transitions associated with symptom amelioration or represent other compensatory neural mechanisms that come online over time. The more individualized, idiographic approach suggested here compliments current approaches by specifically timing imaging acquisition when symptoms are changing most markedly. This approach will generate data whereby clinical researchers can identify neural markers of symptom change proximal to when improvements or decompensation occur, and can advance biological psychiatry toward more personalized approaches to treatment.

CONFLICT OF INTEREST

The author declares no conflict of interest.

REFERENCES

1 Odgers CL, Mulvey EP, Skeem JL, Gardner W, Lidz CW, Schubert C. Capturing the ebb and flow of psychiatric symptoms with dynamical systems models. *Am J Psychiatry* 2009; **166**: 575–582.
2 Hayes AM, Laurenceau J-P, Feldman G, Strauss JL, Cardaciotto L. Change is not always linear: the study of nonlinear and discontinuous patterns of change in psychotherapy. *Clin Psychol Rev* 2007; **27**: 715–723.
3 Vittengl JR, Clark LA, Jarrett RB. Validity of sudden gains in acute phase treatment of depression. *J Consult Clin Psychol* 2005; **73**: 173–182.
4 Tang TZ, DeRubeis RJ. Sudden gains and critical sessions in cognitive-behavioral therapy for depression. *J Consult Clin Psychol* 1999; **67**: 894–904.
5 Hayes AM, Beevers CG, Feldman GC, Laurenceau J-P, Perlman C. Avoidance and processing as predictors of symptom change and positive growth in an integrative therapy for depression. *Int J Behav Med* 2005; **12**: 111–122.
6 Gilboa-Schechtman E, Foa EB. Patterns of recovery from trauma: the use of intraindividual analysis. *J Abnorm Psychol* 2001; **110**: 392–400.
7 Trull TJ, Ebner-Priemer U. The role of ambulatory assessment in psychological science. *Curr Dir Psychol Sci* 2014; **23**: 466–470.
8 Gibbons RD, Weiss DJ, Frank E, Kupfer D. Computerized adaptive diagnosis and testing of mental health disorders. *Annu Rev Clin Psychol* 2016; **12**: 83–104.
9 Poldrack RA, Laumann TO, Koyejo O, Gregory B, Hover A, Chen M-Y *et al.* Long-term neural and physiological phenotyping of a single human. *Nat Commun* 2015; **6**: 8885.
10 Phillips ML, Chase HW, Sheline YI, Etkin A, Almeida JR, Deckersbach T *et al.* Identifying predictors, moderators, and mediators of antidepressant response in major depressive disorder: neuroimaging approaches. *Am J Psychiatry* 2015; **172**: 124–138.