Neuropsychopharmacology www.nature.com/npp

HOT TOPICS

Computational phenotyping and longitudinal dynamics to inform clinical decision-making in psychiatry

Michele Ferrante[1] and Joshua A. Gordon[1]

Neuropsychopharmacology (2021) 46:243–244; https://doi.org/10.1038/s41386-020-00852-z

Computational approaches have the potential to transform mental health research and care. Biophysical modeling of brain mechanisms can inform how neural activity produces behavior. Computational phenotyping can dissect behavior into its components, helping identify their neural bases. Finally, data-driven approaches can lead us to novel diagnostic systems and biomarkers, as well as better individual-level predictors that can guide care with precision.

There is early, suggestive evidence of the promise of such approaches. The B-SNIP study [1] used a data-driven approach to stratify a transdiagnostic sample of 3000 individuals with psychosis into three biotypes with differences in cognitive and social processing, sensorimotor reactivity, and psychosis symptoms. Similarly, a clustering analysis of functional connectivity patterns in ~1000 subjects with depression revealed four biotypes that differ by symptomatology and treatment responses [2]. These studies, based on cross-sectional snapshots of primarily neurobiological data, represent important first steps toward harnessing computational approaches.

To improve upon these efforts, we argue for supporting approaches that integrate additional data types, such as app and sensor-based data. Data inputs should also be refined to align better to the underlying functional structure of behavior. This is where computational phenotyping enters into the equation. Formalizing behavioral constructs with mathematical rigor, computational phenotyping seeks to make hypotheses regarding behavior and test those hypotheses through precise, quantitative predictions. A classic computational phenotype study describes the rules underlying probabilistic reward-based learning, which has been adapted to describe and predict subjective mood [3]. This approach that has led to the demonstration of a robust functional neuroimaging correlate of depression in a recent meta-analysis [4], and inspired a recent clinical trial demonstrating that antagonizing κ-opioid-receptor improves reward-circuit dysfunction as a step along the pathway to developing novel antidepressants [5].

An additional dimension that would enrich these datasets is time. Psychiatric phenotypes are not static, but rather reflect dynamic biological and psychological processes. Datasets need to be not only multimodal but also longitudinal, with sufficient temporal precision to sample this dynamism. Dynamic data visualizations [6] can enable analysis of such datasets to augment discovery and clinical decision-making. Consider the example shown in Fig. 1, which uses a simulated dataset to model the evolution over time of behavioral phenotypes in a sample comprising three different biotypes. Initially, behavioral data from the three biotypes overlap. Over time, however, phenotypic measurements in the three biotypes evolve differently, particularly in response to an intervention.

To maximize the return on our data investments, we must ensure that the phenotypes we measure, and the tools with which we analyze these data, reflect the underlying neurobiological processes and temporal trajectories inherent in the illnesses we seek to understand. Importantly, a longitudinal, deep phenotype approach would leverage individual and group dynamics to predict and inform individual-level treatment-response. This change could allow us to reimagine the design of translational studies and augment our clinical decisions with real-world, just-in-time clinical evidence.

[1]National Institute of Mental Health, NIH, Bethesda, MD 20892, USA
Correspondence: Joshua A. Gordon (joshua.gordon@nih.gov)

Published online: 9 September 2020

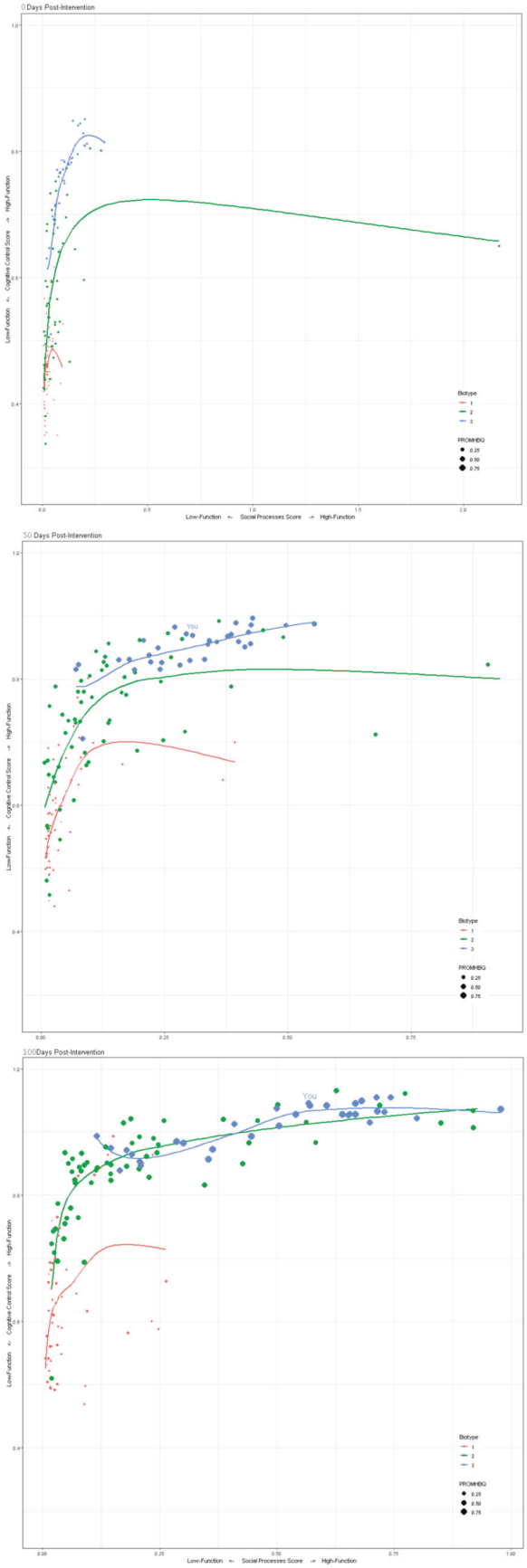

Fig. 1 Still visualization portraying the post-intervention temporal trajectories of three hypothetical biotypes (synthetic data in green, blue, and red) along three Research Domain Criteria (RDoC) neurobehavioral dimensions (a brain-based measure, cognitive control, and social processes task scores). Compare this still visualization with its dynamic version at https://github.com/mferr133/Animate_RDoC/blob/master/Animate_RDoC.gif (see R code used to generate the figure at https://github.com/mferr133/Animate_RDoC/blob/master/Animate_RDoC.R). The visualization displays how a psychiatric intervention may move patient biotypes from a mental health sub-space of low-function (bottom-left region of each graph) to a mental health sub-space of high-function (top-right region each graph). The *x*-axis is adjusted to keep data centered while accounting for the intervention-induced expansion across that dimensional scale (Social Processes), as well as, to show the effect of an "outlier" on the model fitting—at the beginning of the simulation. Individual trajectories are represented in the dynamic version by the moving dots with possibility of adding individualized labels (e.g., You). Each time step in the temporal trajectory is represented as a vector with a direction and an amplitude (acceleration) for each subject. Solid lines of different colors represent the just-in-time, non-linear model fits for the three biotypes. *Loess*, short for Local Regression is the non-parametric approach that was used as model to fit multiple regressions in a local neighborhood. The diameter of each dot represents a brain measure, specifically a PRO-Mental Health Biomarker Quantification (PROMHBQ) score (e.g., a brain oscillation or the strength of the connectivity between two brain regions associated with positive mental health outcomes). Scores have been scaled from 0 (lowest-function) to 1 (highest-function) to compare the simulated data with a theoretical population matched for age, gender, and ethnicity. Top panel: pre-intervention baseline; center panel: 50 days post-intervention; bottom panel: 100 days post-intervention.

FUNDING AND DISCLOSURE

The authors declare that, except for income received from the primary employer, no financial support or compensation has been received from any individual or corporate entity over the past 3 years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential competing interests.

AUTHOR CONTRIBUTIONS

M.F. created the simulation and the figure and wrote the manuscript. J.A.G. wrote the manuscript.

ADDITIONAL INFORMATION

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

REFERENCES

1. Clementz BA, Sweeney JA, Hamm JP, Ivleva EI, Ethridge LE, Pearlson GD, et al. Identification of distinct psychosis biotypes using brain-based biomarkers. Am J Psychiatry. 2016;173:373–84.
2. Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, et al. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. Nat Med. 2017;23:28–38.
3. Rutledge RB, Moutoussis M, Smittenaar P, Zeidman P, Taylor T, Hrynkiewicz L, et al. Association of neural and emotional impacts of reward prediction errors with major depression. JAMA Psychiatry. 2017;74:790–7.
4. Keren H, O'Callaghan G, Vidal-Ribas P, Buzzell GA, Brotman MA, Leibenluft E, et al. Reward processing in depression: a conceptual and meta-analytic review across fMRI and EEG studies. Am J Psychiatry. 2018;175:1111–20.
5. Krystal AD, Pizzagalli DA, Smoski M, Mathew SJ, Nurnberger J, Lisanby SH, et al. A randomized proof-of-mechanism trial applying the 'fast-fail' approach to evaluating κ-opioid antagonism as a treatment for anhedonia. Nat Med. 2020;26:760–8.
6. Pedersen T, Robinson D. gganimate: A grammar of animated graphics. R package version 0.9.9.9999. 2017. http://github.com/thomasp85/gganimate