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Beyond fingerprinting: Choosing predictive connectomes over reliable connectomes

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A B S T R A C T

Recent years have seen a surge of research on variability in functional brain connectivity within and between individuals, with encouraging progress toward understanding the consequences of this variability for cognition and behavior. At the same time, well-founded concerns over rigor and reproducibility in psychology and neuroscience have led many to question whether functional connectivity is sufficiently reliable, and call for methods to improve its reliability. The thesis of this opinion piece is that when studying variability in functional connectivity—both across individuals and within individuals over time—we should use behavior prediction as our benchmark rather than optimize reliability for its own sake. We discuss theoretical and empirical evidence to compel this perspective, both when the goal is to study stable, trait-level differences between people, as well as when the goal is to study state-related changes within individuals. We hope that this piece will be useful to the neuroimaging community as we continue efforts to characterize inter- and intra-subject variability in brain function and build predictive models with an eye toward eventual real-world applications.

In recent years, we have learned that functional brain connectomes are relatively stable within individuals, unique across individuals, and predictive of phenotypes and behaviors such as age (Dosenbach et al., 2010; Liem et al., 2017; Nielsen et al., 2019), cognitive abilities (Cole et al., 2012; Finn et al., 2015; Rosenberg et al., 2016; Sripada et al., 2020; Yamashita et al., 2018), personality (Adelstein et al., 2011; Dubois et al., 2018a; Hsu et al., 2018; Nostro et al., 2018), and clinical symptoms (Emerson et al., 2017; Fair et al., 2013; Lake et al., 2019; Plitt et al., 2015; Wang et al., 2020). Based on this line of work, many researchers are optimistic that functional connectivity profiles, or "fingerprints", could eventually serve as biomarkers with real-world applications (Castellanos et al., 2013; Finn & Constable, 2016; Gabrieli et al., 2015; Sui et al., 2020; Woo et al., 2017). On the other hand, the ongoing replication crisis in psychology and neuroscience has led the field to turn a critical lens on the reliability of the signals we measure with functional magnetic resonance imaging (fMRI). Concerns over rigor and reproducibility of neuroimaging-derived measures have spurred efforts to test for and report unreliability (i.e., uncover the extent of the "problem"), and develop acquisition and analysis pipelines to improve reliability (i.e., solve the "problem").

Minimizing measurement error is a laudable goal for virtually any scientific endeavor. But has the field of human neuroimaging been too quick to see imperfect reliability as problematic? When it comes to brains, minds, and behavior, we cannot necessarily attribute variability to simple measurement error. Put another way, optimizing for within-subject reliability, or fingerprinting, does not always mean optimizing for meaningful information. While the two may sometimes overlap, increased reliability does not necessarily entail improved behavior prediction, and vice versa.

Ultimately, the utility of connectome fingerprints will not be for individual identification per se, but rather for understanding and predicting behavior. Therefore, we argue that rather than optimizing for reliability in connectomes themselves (i.e., brain-to-brain) and assuming (hoping) that this will lead to improved sensitivity to behavioral measures, we should optimize for connectome-based prediction (i.e., brain-to-behavior) from the start[1]. In what follows, we present theoretical and empirical evidence to support this perspective, both when the goal is to predict relatively stable individual differences (part 1) as well as to predict within-subject change (part 2). Rather than chasing reliability for its own sake, benchmarking studies using behavior prediction (e.g., Dadi et al., 2019; Pervaiz et al., 2020; Taxali et al., 2021; Kashyap et al., 2019; Kong et al., 2021) will accelerate our understanding of not just what differs within and across individuals, but why—in other words,

[1] Researchers may focus on optimization at one or more stages of a neuroimaging study, including data acquisition (e.g., field strengths, sequence parameters, scan conditions [rest, task, etc.]), individual-participant data analysis (e.g., preprocessing pipeline, single-subject modeling and/or dimensionality reduction steps), and analyses involving multiple participants (e.g., additional hierarchical models involving group-level information, choice of classification/prediction algorithms). Any of these steps could theoretically be optimized for either reliability or behavior prediction; we argue broadly for the latter.

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which features of the connectome remain consistent over time, reflecting stable traits, and which features vary with changing states.

1. Unique is not necessarily meaningful, and meaningful is not necessarily unique

Well-founded concerns over reproducibility have led to scrutiny of statistical practices and so-called "researcher degrees of freedom" in neuroimaging studies. At the same time, the many branch points in the decision tree of neuroimaging data analyses give rise to a multiverse of pipelines for any given dataset, which can yield somewhat different results (Botvinik-Nezer et al., 2020). For many of these branch points, there is either little theoretical basis to prefer one option over others, or competing theoretical bases for different options. Lack of theory and competing theories each carry their own challenges, leading some researchers to argue that the optimal pipeline(s) should be determined empirically based on a chosen metric. One such metric is test-retest reliability: we should prefer the pipeline that yields the most similar results across different measurements from the same unit of interest—in this case, individuals.

On its face, this idea has intuitive appeal. Indeed, there is a substantial literature beginning more than two decades ago (Casey et al., 1995; Ramsey et al., 1996; Rombouts et al., 1997) that uses measures such as the intra-class correlation coefficient (ICC) to evaluate the stability of fMRI-based individual measures and argues, explicitly or implicitly, that maximizing similarity of measures taken from the same person over time is the most desirable outcome (though see Noble et al. (2019) and Noble et al. (2021) for recent reviews of functional connectivity reliability and the importance of considering validity). Indeed, test-retest reliability is often used as a benchmark for new developments in acquisition and/or analysis (Zuo et al., 2019): increased reliability indicates an improved method, no questions asked. Our "functional connectome fingerprinting" paper (Finn et al., 2015), in which we demonstrated that individuals could be identified—i.e., discriminated from one another—based on whole-brain functional connectivity profiles acquired during different sessions and cognitive tasks, inspired a new angle on this line of work. Many subsequent studies, including some of our own, have directed efforts at exploring the limits of fingerprinting (Airan et al., 2016; Finn et al., 2017; Horien et al., 2018; Jalbrzikowski et al., 2020; Waller et al., 2017), characterizing the source of the most identifying information (Byrge and Kennedy, 2019; Peña-Gómez et al., 2018), and/or improving fingerprinting accuracy through improved pipelines (Abbas et al., 2020; Amico & Goñi, 2018; Bari et al., 2019; Chen & Hu, 2018; Li and Atluri, 2018; Sarar et al., 2021; Shojaee et al., 2019; Wang et al., 2019).

But why do we care about individual differences in neuroimaging measures in the first place? Most researchers are probably not interested in brain-based fingerprinting for its own sake; after all, there are better ways to identify someone than going to the trouble to scan them and calculate a brain connectivity profile (e.g., DNA, actual fingerprints, simply looking at or speaking to them). Rather, most of us are interested in individual differences in brain function for their relationship to psychological constructs and/or behavior. Investigators may be motivated to characterize these relationships to answer basic scientific questions (e.g., testing parametric hypotheses about where and when certain cognitive processes are reflected in neural activity) and/or for practical purposes (e.g., with an eye toward developing imaging-based biomarkers of present or future clinical outcomes). Most studies take as their premise, again either explicitly or implicitly, that increased reliability indicates increased utility of personalized connectomes for some other purpose, i.e., behavior prediction or diagnostic status classification (Finn and Constable, 2016; Gratton et al., 2020; Parkes et al., 2020; Waller et al., 2017).

But this does not necessarily follow, theoretically or empirically. If connectomes are akin to bar codes—random patterns that are one-of-a-kind, but have no relationship to any feature of the individual they identify—one could have high fingerprinting accuracy with low utility for behavior prediction. In other words, connectomes could be unique but unrelated to anything interesting (high reliability, low validity). On the other hand, if connectomes do share variance with real-world variables, if a matching algorithm consistently mistakes one subject for another subject with the same or similar behavior score, one could have low(er) fingerprinting accuracy but high(er) utility for behavior prediction; in other words, connectomes could be not entirely unique, but the overlap between individuals could be a byproduct of the useful information they contain (low[er] reliability, high[er] validity). See Fig. 1 for a schematic of these theoretical scenarios.

From a theoretical stance, then, optimizing fingerprinting accuracy does not necessarily entail optimizing utility for behavior prediction. What about empirically? Increased fingerprinting could still be a useful proxy for improved behavior prediction, even if the two outcomes are conceptually distinct. After all, it would be surprising if one could achieve good prediction accuracy without some minimum level of reliability. However, the literature on this is mixed. While some studies report that improving fingerprinting entails a corresponding improvement in behavior prediction (Amico and Goñi, 2018; Elliott et al., 2019), or that the same networks that are most distinguishing of individuals also tend to be the most related to behavior (Finn et al., 2015), other studies find little to no relationship between the reliability of connections and their utility for behavior prediction (Byrge and Kennedy, 2020; Liu et al., 2018; Mantwill et al., 2021; Noble et al., 2017). Noble et al. (2017) report only a very weak correlation ($r = 0.05$) between an edge's test-retest reliability and its relevance for behavior (fluid intelligence in this case, which is relatively stable within and across individuals). Related work has shown that the brain states in which people are more identifiable are not necessarily the best brain states for predicting behavior (cf. Finn et al., 2017; Greene et al., 2018). A recent paper proposing a new statistic for quantifying relative similarity within versus across individuals, discriminability, found that discriminability was a useful proxy for effects of sex and age (Bridgeford et al., 2020), though effect sizes were modest compared to studies that demonstrated direct prediction/classification of age and sex without optimizing for test-retest reliability first (Nielsen et al., 2019; Weis et al., 2020; Zhang et al., 2018). In parallel to this mixed literature, there is an emerging consensus that information that identifies individuals and information that predicts behavior are both highly distributed throughout the connectome (Byrge and Kennedy, 2019; Dubois et al., 2018b; Pannunzi et al., 2017). It could be the case that some minimum level of distributed reliability is necessary for accurate behavior prediction, at least for trait-level phenotypes. But the weaker-than-expected relationship between reliability and behavior prediction—both in specific edges (univariate) and the overall connectome (multivariate)—does suggest that by optimizing for fingerprinting first, we risk becoming stuck in local maxima for behavior prediction, when in fact we would be better served by optimizing for behavior prediction from the start.

Optimizing for fingerprinting accuracy without regard to behavioral relevance also creates at least two perverse incentives that can bias even well-intentioned studies. First, if connectome fingerprints are not perfect—which they're not—we should expect fingerprinting accuracy to decrease in larger sample sizes, due to the higher chance of including similar pairs of subjects (Waller et al., 2017). Methods for boosting fingerprinting will thus have an easier time proving their significance in smaller datasets, but may not generalize to a wider population. On the other hand, a valid behavior prediction model should only get more accurate when trained on a larger sample.[2] Second, any factor that affects fMRI data, is unique to individuals, and is stable across time—whether

[2] In practice, in the published literature, behavior prediction effect sizes often appear to decrease with sample size when looking across datasets, but this is likely due in large part to a wider variance in effect sizes in small samples combined with publication bias (Marek et al., 2020). Within datasets, provided data are harmonized and there are no systematic biases between the target of predic-

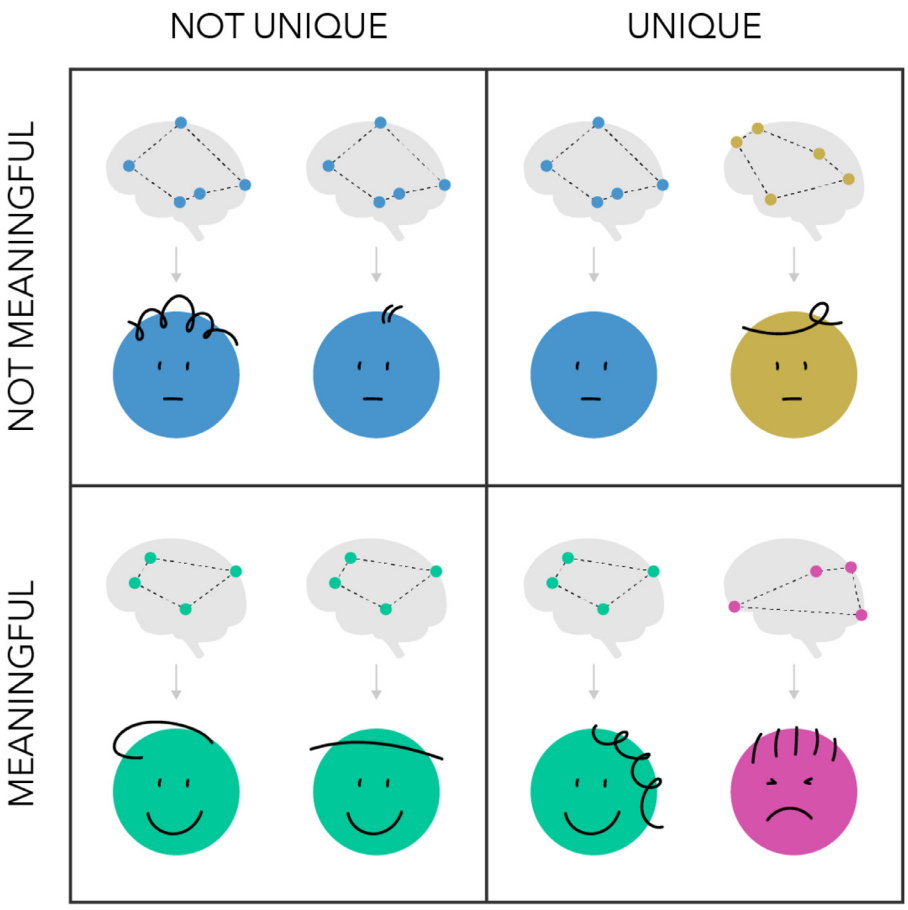

Fig. 1. Uniqueness does not imply meaningfulness, and vice versa. Schematic depicting why uniqueness and meaningfulness are orthogonal features. The upper left panel (not unique or meaningful) depicts a theoretical scenario in which two individuals have highly similar connectomes, but no shared behavior explains this overlap. The upper right panel depicts a scenario in which connectomes are unique but not meaningful, akin to bar codes, where the pattern of connections is one-of-a-kind but arbitrary (i.e., unrelated to any features of the individual it represents). The lower left panel depicts a scenario in which connectomes are not unique but are meaningful: two individuals have very similar connectomes such that they might be mistaken for one another in identification experiments, but these individuals are also similar in one or more behavioral domains (in this case, positive mood), such that this particular pattern of connections might index mood. In this scenario, connectomes carry relevant information that could be used to predict behavior. Finally, the lower right panel depicts a scenario in which connectomes are both unique and meaningful: two individuals have distinct connectomes and distinct emotional states.

meaningful or not—will boost fingerprinting accuracy. This includes differences in anatomy, functional anatomy[3], magnetic field distortions due to head shape, etc. In other words, it is possible to get good fingerprinting for the "wrong" reasons. With behavior prediction, these factors could only boost accuracy if they systematically covary with the behavior of interest. Of course, there are many examples of such covariation: head motion is probably the most notorious (Siegel et al., 2017), but anatomy and functional anatomy also covary with many variables of interest (e.g., age, diagnostic status). The difference is that in fingerprinting, it is almost a given that these things will help, whereas in behavior prediction, they may variably help or hurt, or not have any effect. (While not necessarily endorsed by these authors, the utilitarian view that prediction is a black box and we should value accurate prediction regardless of what drives it is also more defensible in the case of behavior prediction, since it has real-world utility; fingerprinting is reduced to an uninteresting tautology from this perspective.)

On a deeper level, functional connectomics, while a powerful way to characterize the brain, suffers from an absence of ground truth. What does the biological functional connectome look like? Are connections binary (present or not), or are they weighted? If weighted, how do we define weights? This means even when we do achieve similar results across multiple measurements, we cannot necessarily infer that the reconstructed network more closely reflects the "true" underlying network. This lack of a known target, combined with the noise inherent to fMRI and functional connectivity in particular, make it unrealistic to expect that we will ever achieve perfect reliability and validity. Of course, to the extent that it is possible to identify pure noise in our data, we wholeheartedly support efforts to characterize and remove it. But when it comes to the brain, what appears to be noise can often become meaningful signal when combined with the right additional measurements (Uddin, 2020); this is the focus of the next section.

2. We're not perfectly stable, so why should our functional connectomes be?

Recent work reported an individual-identification algorithm so accurate that, based on patterns of salient "keypoints" in T1-weighted brain scans, it identified previously unknown instances of mislabeled participants in large, open-access MRI datasets (Chauvin et al., 2020). Impressively, by identifying keypoint signatures robust to scan-to-scan variation, the algorithm matched MR images from an individual collected as many as 11 years apart.

What makes the keypoint signature patterns so well suited for identifying individuals, however, likely makes them ill suited for identifying states. Because measures that are maximally stable across repeated observations are, by definition, minimally sensitive to intra-individual change, a model based on keypoint signatures may be able to identify a person but fail to, for example, predict cognitive changes with aging. (The same logic would follow if the keypoint signature pattern were based on functional rather than structural brain measures.)

Of course, not all variance in functional connectivity reflects behaviorally meaningful change. The keypoint signature example, however, highlights the costs of prioritizing measurement reliability—that

tion and other confounding variables, prediction accuracy should increase with training set size (up to some noise ceiling; Cui & Gong, 2018).

[3] Functional anatomy refers to the location of specific functional specialization profiles along an anatomical substrate. For example, even if two subjects have identical cortical folding patterns in a given brain region (same anatomy), there could be differences in how functions map on to this anatomy—in other words, which specific patches along that cortical surface are most responsive to given inputs and/or outputs (functional anatomy).

is, optimizing fingerprinting—at the expense of other considerations: Our brains are always changing (as they must, given our ever-changing behavior; Waschke et al., 2021), and discarding measures that are sensitive to this change will frustrate our ability to predict meaningful variation in cognition over time.

Changing cognitive states have so far not been the focus of functional connectivity-based prediction. Since emerging a decade ago, the approach has largely been applied to capture differences between individuals as described in part 1. Although individual differences research has an influential history in psychology and offers insights into mental processes and the brain systems that underlie them, its predominance in cognitive network neuroscience is likely as much due to the availability of datasets with many participants (rather than many hours of scan time per participant)[4] as it is for its theoretical and practical utility.

Despite the emphasis on individual differences in functional connectivity research, as psychologists and neuroscientists, we are almost always interested in mental processes that vary within individuals. It is just as useful and interesting to predict when attention fluctuates, memory fails, and emotion regulation flounders as it is to predict a person's overall attention, memory, and emotional regulation abilities. In fact, it is arguably more useful to predict state-like aspects of behavior: Cognitive processes including attention (Fortenbaugh et al., 2015; Robertson et al., 1997) and working memory (deBettencourt et al., 2019) can fluctuate dramatically[5] with serious consequences for ongoing behavior, and clinical symptomatology is rarely consistent across the lifespan. Within-subject prediction is gaining traction with the growing enthusiasm for and availability of datasets with high-frequency or longitudinal sampling of brain function and behavior—so much so that "deep imaging" for personalized neuroscience is the focus of a recent special issue of *Current Opinion in Behavioral Sciences*.

Imagine that you have collected a sample in which thousands of participants were scanned hundreds of times each. You generate functional connectivity matrices for each scan session using a hypothetical pipeline that results in perfect fingerprinting accuracy and (although we emphasized in the previous section that such matrices would not necessarily predict behavior) perfect prediction of individual differences in working memory capacity. How successful would these fingerprints be for predicting states rather than people? For example, would they capture fluctuations in working memory from one task trial to the next? Improvements in working memory after a surprisingly successful intervention? Changes in capacity across development? Using this example as a jumping-off point, here we discuss how connectome fingerprints can reflect—or obscure—meaningful changes in mental states across repeated observations separated by moments to days to years.

2.1. Short time-scale predictions (i.e., within fMRI runs)

So far we have implicitly focused on functional connectome fingerprinting techniques that take as input run-specific or session-specific functional connectivity matrices. Connectivity matrices, however, can also be calculated from subsets of BOLD signal time series from a single run. Subsets are typically defined with data-driven approaches that apply sliding windows (e.g., Gonzalez-Castillo et al., 2015; Sakoğlu et al., 2010) or detect hidden states (e.g., with Hidden Markov modeling; Ou et al., 2015; Robinson et al., 2015; Shappell et al., 2019) or change-point estimation (Cribben et al., 2012; Xu and Lindquist, 2015); see Lurie et al., 2020 for a recent review). Subsets can also be defined with hypothesis-driven approaches such as those that divide time series based on features of a cognitive (Rosenberg et al., 2020) or naturalistic (Finn and Bandettini, 2020) task. Recent work has even obviated the need for subset definitions in some cases, validating "instantaneous" measures such as change-point connectivity requiring two consecutive TRs (Ramot and Gonzalez-Castillo, 2019) and edge-centric connectivity reflecting concurrent fluctuations in pairs of nodes at every TR (Esfahlani et al., 2020; Faskowitz et al., 2020).

Regardless of how subsets of data are selected, generating multiple functional connectivity matrices per fMRI run allows us to ask whether within-run changes in connectivity are associated with concurrent changes in behavior. Of course, functional connectomes can vary for more or less interesting reasons, which is why validating connectivity dynamics with "ground truth" measures of mental states (ongoing task performance, eye-tracking data, experience sampling responses, etc.) is so crucial (Song and Rosenberg, 2021). Although optimizing for stable sub-run connectomes would minimize the variance due to uninteresting causes such as sampling variability and head motion (Laumann et al., 2017), it also would dampen any variance due to interesting causes. Rather than strive to maximize fingerprinting accuracy, we should strive to supplement our fMRI data with densely sampled behavioral and/or physiological measures and test replication of observed connectivity-behavior relationships in new individuals and datasets (Poldrack et al., 2020; Scheinost et al., 2019).

In addition to informing how behavioral states emerge from brain network dynamics, relating connectivity to behavior on short timescales can help address a fundamental question in connectome-based prediction: Why can we predict behavior from resting-state data? Well-replicated results in the field demonstrate that predictions can be generated from fMRI data acquired in the absence of an explicit task. The implications are intriguing: We don't need to, for example, give someone an attention task—or any task for that matter—to measure how well they pay attention overall (Kessler et al., 2016; Poole et al., 2016; Rosenberg et al., 2016; Wu et al., 2020). Is this because "intrinsic" functional brain organization reflects attentional abilities? Because individuals with stronger and weaker sustained attentional abilities are engaged in systematically different cognitive states during rest? A combination of the two? Although work has taken care to rule out potential confounds such as in-scanner motion as drivers of this effect, the question remains largely unresolved. Looking ahead, we are unlikely to discover the answer if, as a field, our sole success metric for functional connectivity processing pipelines is fingerprinting accuracy, a proxy—albeit an imperfect one—for connectome reliability.

2.2. Medium time-scale predictions (i.e., hours to days to weeks)

Those who agree that characterizing connectivity dynamics is worthwhile and important may still argue that,when it comes to static functional connectivity matrices,the more reliable the better. Reliability metrics, however, disregard the fact that not all scan-to-scan variability is noise. For example, although evidence suggests that traits rather than states dominate functional network organization, the interaction between a person's identity and the task they are performing explains about 20% of the variance in similarity between functional networks observed during different fMRI runs in the Midnight Scan Club dataset (Gratton et al., 2018). This individual-by-task interaction, reflecting meaningful scan-to-scan variability in the form of an individual-specific state effect, is the third-largest source of variance in network similarity after group and participant identity, each of which explain about 35-40% of the variance in network similarity. Complementary work has demonstrated that functional networks—and even node boundaries themselves (Salehi et al., 2020)—vary across scan runs and sessions with factors including internal states (e.g., attention; Rosenberg et al., 2020) and pharmacological agents (e.g., caffeine; Wong et al., 2012).

Because states explain less variance in functional connectivity patterns than do traits, elucidating reliable state-specific patterns

[4] For a plot of the number of participants and scan hours per individual in current publicly available fMRI datasets, see Naselaris et al. (2021).

[5] Further underscoring the importance of cognitive performance fluctuations, intra-individual differences in behavior may in some cases explain inter-individual differences. For example, what distinguishes individuals with higher and lower working memory capacities is not the maximum number of items they can hold in mind, but rather how often they successfully maintain that maximum in memory (Adam et al., 2015).

will require substantial amounts of data per individual and cognitive/behavioral state of interest. Furthermore, as with dynamic connectivity analyses, it will be critical to validate connectivity changes observed across days to weeks with observed "ground truth" changes in behavior, and to replicate results across novel individuals and datasets.

Although improving session-to-session functional connectivity reliability is important for certain research questions, if functional connectivity is ever to be used in real-world settings to evaluate clinical symptom trajectories or treatment or intervention efficacy, we should also aim to capture reliable changes in connectivity over timescales relevant to these processes. One might imagine that large swings in symptoms over days to weeks within an individual—e.g., whether a patient with bipolar disorder is currently euthymic or in the throes of a manic episode—could account for substantial variance in connectivity, just as task manipulations do in healthy volunteers (Gratton et al., 2018). Given that one ultimate goal of connectome-based prediction is to inform clinical decision making, scan-to-scan variability should not be dismissed as noise out of hand.

2.3. Long time-scale predictions (i.e., months to years)

Studies are beginning to characterize functional connectome stability across developmental time. Recent work, for example, demonstrated successful connectome fingerprinting using scans separated by one to two years in development, with modest success for scans separated by three years (Horien et al., 2019). Although this work provides valuable insight into the stability of functional brain organization across years, it is important to consider what realistic ceiling on functional connectome fingerprinting accuracy we should expect for longitudinal data given widespread changes in brain structure and function across the lifespan—from infancy to childhood, adolescence, younger adulthood, and older adulthood (Casey et al., 2005; Cox et al., 2016; Giedd et al., 1999; Hedman et al., 2012; Knickmeyer et al., 2008; Mills et al., 2016). Introducing techniques to maximize identification using scans separated by months to years may, depending on participants' ages, conceal meaningful developmental change. Instead, measuring the aspects of functional connectivity patterns that do and do not vary with development, aging, and cognitive changes across the lifespan can inform behaviorally meaningful trajectories of functional brain organization[6]. Characterizing longitudinal change in connectivity patterns and behavior may also help us overcome a limitation of nearly all connectome-based predictive modeling work to date: that it is technically postdiction, estimating behavior that has already been measured. In other words, tracking reliable connectome trajectories in development and aging may allow us to better forecast future outcomes and improve the real-world utility of connectome-based prediction.

2.4. Predicting behavioral states with connectivity traits

Automatically dismissing variable functional connectomes as scientifically uninteresting is misguided because what appears to be "unreliability" may in fact reflect changing mental states. It is an open question, however, whether connectome dynamics are necessary and/or sufficient for predicting behavior dynamics. In many cases they may not be. For example, a single measure of static functional connectivity observed early in development may predict risk for or resilience to psychopathology, and trait-like aspects of the connectome may predict response to treatment . It may also be the case that brain dynamics observed over one timescale predict behavior dynamics across another (e.g., perhaps short-term functional connectivity dynamics during an emotional movie predict mood disorder symptom trajectories over a longer term). Testing different models using trait- and state-like aspects of functional connectivity to predict trait- and state-like aspects of behavior can shed light on which aspects of the functional connectome are necessary and sufficient for predicting a given behavior of interest.

3. Choosing the right behavior(s)

Throughout this article, we have focused on the brain side of the brain-behavior equation, arguing that we should optimize our brain measures to be maximally sensitive to behavior, broadly defined. But which behavioral measures are most important? How meaningful are these measures? Although the behavior side of the equation often gets much less attention from neuroimagers, it is perhaps even more important for building reliable, valid predictive models. We often use targets of convenience, i.e., self-report and lab-based tasks that are collected alongside neuroimaging data, to establish proof-of-principle for a brain-behavior relationship. Yet both recent and longer-standing work calls into question the reliability and construct validity of many of these measures as they are typically used (Eisenberg et al., 2019; Hedge et al., 2018; Spearman, 1910).

However, recent developments give reason to be optimistic on this front. First, in computational phenotyping, rather than take task-elicited measures (e.g., accuracy, reaction time) at face value, computational models are fit to derive a set of latent variables that characterize a person's behavior or "style" on one or more tasks (Patzelt et al., 2018, Montague et al., 2012, Wiecki et al., 2015, Schwartenbeck and Friston, 2016). This approach can offer more mechanistic insights into behavioral tendencies that may be shared across a variety of cognitive and affective domains (Thompson et al., 2019). Still, it is early days for many of these models, and we will need to assess their longer-term construct validity just as we do for more traditional measures. Second, digital phenotyping, in which data are harvested from smartphones and other devices (e.g., levels of movement and sociality, location, voice and text analysis) to provide a picture of activity "in the wild", is another promising source of behavior prediction targets to understand the bidirectional relationship between brain and behavior (Insel, 2017, Heller et al., 2020). Finally, as mentioned in the previous section, longitudinal prediction of clinical and other real-world outcomes will be the true translational test for this line of work. This will likely require integration with health system medical records, which will pose privacy challenges, but will be necessary for any eventual applications.

In the meantime, although the "correct" targets for prediction remain an open question, this should not diminish our commitment to benchmarking functional connectomes according to some kind of relevance for behavior. Focusing on behavior prediction will encourage neuroimaging researchers to stay abreast of the latest developments in these fields, and promote valuable cross-talk between behavior- and brain-based phenotyping efforts.

4. Conclusions

If perfect functional connectome fingerprinting implies perfect stability in brain function and mental life, it is neither a realistic nor a desirable goal. Now, the more pressing challenges are to optimize connectivity patterns for behavior prediction, isolate trait-like and state-like connectivity components (Song and Rosenberg, 2021), and tease apart state variability reflecting signals of interest from those of no interest. In the future, with more neuroimaging and behavioral data per individual, we may be able to optimize for state-specific fingerprinting accuracy. Until then, optimizing fingerprinting will not necessarily improve behavior prediction or advance understanding of relationships between the brain and the mind.

[6] Longitudinal analyses face unique methodological challenges, such as data points that are not missing at random and measurements whose validity and error varies over time. Models of developmental change must also account for complex nonlinear trajectories in brain function and behavior. Recent work provides new approaches to and recommendations for longitudinal data analysis in developmental cognitive neuroscience (e.g., Kievit et al., 2018; King et al., 2018) that can inform long time-scale predictions of behavior from fMRI data.

Declaration of Competing Interest

The authors declare no competing financial interests.

Credit authorship contribution statement

Emily S. Finn: Conceptualization, Writing – original draft, Writing – review & editing. **Monica D. Rosenberg:** Conceptualization, Writing – original draft, Writing – review & editing.

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Data and code availability statement

This article is a review/opinion piece and does not use any empirical data or code.

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