Idiosynchrony: From shared responses to individual differences during naturalistic neuroimaging

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Abstract

Two ongoing movements in human cognitive neuroscience have researchers shifting focus from group-level inferences to characterizing single subjects, and complementing tightly controlled tasks with rich, dynamic paradigms such as movies and stories. Yet relatively little work combines these two, perhaps because traditional analysis approaches for naturalistic imaging data are geared toward detecting shared responses rather than between-subject variability. Here, we review recent work using naturalistic stimuli to study individual differences, and advance a framework for detecting structure in idiosyncratic patterns of brain activity, or “idiosynchrony”. Specifically, we outline the emerging technique of inter-subject representational similarity analysis (IS-RSA), including its theoretical motivation and an empirical demonstration of how it recovers brain-behavior relationships during movie watching using data from the Human Connectome Project. We also consider how stimulus choice may affect the individual signal and discuss areas for future research. We argue that naturalistic neuroimaging paradigms have the potential to reveal meaningful individual differences above and beyond those observed during traditional tasks or at rest.

Keywords: individual differences, naturalistic, inter-subject correlation, fMRI, behavior, representational similarity analysis

1 **Highlights**

- 2 • Review literature using naturalistic paradigms to study individual differences
- 3 • Discuss potential utility of idiosyncratic time-locked responses (“idiosynchrony”)
- 4 • Outline technique of inter-subject representational similarity analysis (IS-RSA)
- 5 • Apply IS-RSA to reveal brain-behavior relationships during movie watching
- 6 • Consider role of stimulus selection and other directions for future work

1. Introduction

At present, there are two exciting movements afoot in cognitive neuroscience. First, the field is shifting focus from the group to the individual: instead of combining data across subjects to draw population-level inferences, studies are isolating brain function in single subjects and how it relates to behavioral phenotypes (Bartolomeo et al., 2017; Dubois and Adolphs, 2016; Seghier and Price, 2018). Second, researchers are embracing the complexity of so-called “naturalistic” stimuli—e.g., film clips, spoken narratives—as experimental paradigms, to complement and extend the tightly controlled, parametric tasks that form the pillars of classical psychology work (Sonkusare et al., 2019).

While each of these movements has brought promising discoveries on its own, studies at the intersection—i.e., that use naturalistic stimuli to study individual differences—are relatively uncommon. Why might this be? Naturalistic stimuli evoke patterns of brain activity that are, by and large, highly consistent across subjects (Hasson et al., 2010; Hasson et al., 2004), and typically, naturalistic imaging data are collected and analyzed in ways geared toward detecting similarities between subjects rather than differences (Nastase et al., 2019). Adapting naturalistic tasks to study individual differences and brain-behavior relationships raises several challenges, demanding new approaches to both experimental design and data analysis. The potential payoff, however, is high. Naturalistic tasks offer a “happy medium” between the extremes of highly controlled cognitive tasks, which often lack ecological validity, and resting-state acquisitions, which are entirely unconstrained, making them vulnerable to confounds and difficult to interpret (Vanderwal et al., 2018). They allow experimenters to probe intermingled signals throughout the hierarchy of neural systems—from low-level sensory processing up to social cognition—using data from a single acquisition, and while the brain is engaged in activities more similar to everyday life. Thus, they may offer more “bang for the buck” than either rest or traditional tasks for characterizing spatiotemporal patterns of brain activity in individual subjects.

Here, our goals are threefold. In the first section, we briefly describe the inter-subject correlation (ISC) family of approaches to analyzing naturalistic imaging data, which exploit the time-locked nature of the task across subjects to isolate brain activity driven by the stimulus (Hasson et al., 2004; Nastase et al., 2019). Also in this section, we review existing literature using ISC to study

individual differences. (For comprehensive reviews on naturalistic tasks and inter-subject correlation more generally, we refer the reader to (Sonkusare et al., 2019) and (Nastase et al., 2019), respectively. Our focus here is specifically on how these intersect with the study of individual differences.) In the second section, we advance a framework for studying how individual differences shape brain responses during naturalistic stimulation, a phenomenon we call “idiosynchrony”. We focus specifically on the emerging technique of inter-subject representational similarity analysis (IS-RSA), which adapts ISC to highlight stimulus-driven responses that are idiosyncratic rather than shared. We present the theory behind IS-RSA, then apply it to data from the Human Connectome Project to demonstrate how brain responses during movie viewing share structure with behavioral traits, including working memory and personality. In the final section, we outline directions for future work, including how idiosynchrony might be further adapted to serve as predictive model, and how we might choose stimuli to amplify behaviorally relevant individual signals.

2. Inter-Subject Correlation: Stimulus-locked, fewer assumptions

Because naturalistic paradigms sit somewhere between resting state and traditional tasks, researchers have at their disposal a wide variety of analysis approaches. The presence of a stimulus permits classic techniques for detecting activation to specific features of the stimulus, such as the general linear model (GLM). At the same time, thanks to their continuous, non-parametric nature, these paradigms also lend themselves to approaches developed primarily for rest—for example, functional connectivity, which considers correlations in signal fluctuations between regions, rather than magnitude of activation in any single region.

We place these approaches in a landscape with two major axes: how time-locked to the stimulus they are, and how many assumptions they require. Functional connectivity (FC)—especially static FC, which collapses across the whole time series—demands relatively few assumptions, but is impossible to map back onto the stimulus, and therefore fails to separate stimulus-driven from stimulus-independent sources of neural activity. Dynamic FC gets closer to a time-resolved signal, but in most cases the need for windows of a minimum length makes it difficult to map connectivity fluctuations to specific events within the stimulus, and resulting signals still contain a mixture of stimulus-related and stimulus-unrelated variation within each subject.

GLM-based analyses do capitalize on the “ground truth” of a stimulus with known timing, but in doing so make two critical assumptions: one, that the experimenter knows which features of the stimulus are important for driving brain activity, and two, that they have modeled these features accurately. Non-optimal assumptions at either step will impair sensitivity.

The inter-subject correlation (ISC) family of approaches (Hasson et al., 2004; Nastase et al., 2019; Simony et al., 2016), developed specifically for naturalistic paradigms, maximize sensitivity to stimulus-driven activity with fewer assumptions. These approaches use one subject’s brain activity as a model for a second subject’s brain activity, reasoning that as long as two subjects receive the same input at the same time, any shared variance must be due to stimulus processing. Unlike FC, ISC isolates stimulus-driven signal and is interpretable with respect to events in the stimulus itself. And unlike GLM-based approaches, even if the experimenter doesn’t know—or can’t model—the most important features of the stimulus, as long as there is some consistent signal across subjects, ISC will recover it (Pajula et al., 2012). Thus, ISC is a powerful, data-driven technique for detecting shared responses, anticipated or otherwise.

2.1 Adapting ISC to an individual-differences framework

The classic formulation of ISC assumes that the signal observed at each voxel x and timepoint t reflects a mixture of three components. Loosely following the notation of Nastase et al. (2019), these components are:

c , a stimulus-evoked response that is consistent across subjects

id , a stimulus-evoked response that is idiosyncratic to each subject

ϵ , a noise component (which may reflect both neural activity that is unrelated to the stimulus, i.e., mind-wandering, as well as noise from non-neural physiological and scanner sources)

Thus, for a given subject i the response in voxel x at timepoint t can be described as follows:

$$x_i(t) = c(t) + id_i(t) + \epsilon_i(t)$$

In this formulation, it is not possible to distinguish *id* from ε , unless subjects are exposed to the same stimulus multiple times. Even then, results must be interpreted with caution, because repetition can change how a stimulus is processed. Another approach is to anchor *id* to some other known information about each subject, like a behavioral score (*b*), and search for structure in these responses across subjects:

$$x_i(t) = c(t) + \mathbf{b}_i(id(t)) + \varepsilon_i(t)$$

$$x_j(t) = c(t) + \mathbf{b}_j(id(t)) + \varepsilon_j(t)$$

...

$$x_n(t) = c(t) + \mathbf{b}_n(id(t)) + \varepsilon_n(t)$$

Notice that now the *id* term has lost its subject subscript, since we are assuming that there is some canonical response associated with a given behavior, and each subject's behavioral score acts as a sort of bias term governing to what degree a subject expresses that response.

This framework let us distinguish stimulus-related responses in individual subjects from stimulus-unrelated noise, and does so in a way that facilitates interpretation, since we are linking idiosyncratic responses to a known behavioral measure. Generally, we might predict that the influence of individual differences on $x(t)$ —that is, the ratio of *id* to *c*—grows as one moves up the cortical processing hierarchy, such that the shared, behavior-independent signal dominates in unimodal cortex, while the idiosyncratic, behavior-dependent signal becomes stronger in higher-order association cortex. This may explain why ISC is traditionally high in primary visual and auditory cortex, and drops off (but doesn't necessarily disappear completely) in areas of prefrontal cortex, for example: it is not the case that these regions are not responding to the stimulus, but rather that they respond with different spatiotemporal signatures across subjects (Chang et al., 2018; Hasson et al., 2010). Some of this variance might be explained by trait-level phenotypes.

3. Existing work on ISC & individual differences

1 Despite the traditional focus on shared responses, in recent years, researchers have begun to
2 investigate how ISC varies with both state-level factors related to either the stimulus or
3 experimental instructions, and—more relevant for our purposes—with trait-like factors intrinsic
4 to the subjects themselves.

5
6 Several studies have shown that ISC is sensitive to features of the stimulus (Dmochowski et al.,
7 2014; Hasson et al., 2010; Nummenmaa et al., 2014; Schmälzle et al., 2015). Other studies have
8 kept the stimulus constant and used behavioral priming to show that ISC is sensitive to explicit
9 manipulations of attention or prior beliefs about a stimulus (Cooper et al., 2011; Lahnakoski et
10 al., 2014; Yeshurun et al., 2017). While informative, these studies do not examine why different
11 individuals often spontaneously—i.e., with no explicit priming—show different neural or
12 behavioral responses to the same stimulus.

13
14 A handful of studies have reported spontaneous individual differences in time-locked activity to
15 a stimulus that relate to behavioral appraisal of the stimulus. Using emotional clips, comedy
16 videos, and moral dilemma scenarios, respectively, Nummenmaa et al. (2012), Jaaskelainen et al.
17 (2016) and Tei et al. (2019) found that ISC in certain brain regions correlated with similarity of
18 post-hoc behavioral ratings (of dynamic valence/arousal, humor, and moral conflict) across pairs
19 of subjects. Using an abstract video of animated shapes and an audio story, respectively, Nguyen
20 et al. (2019) and Saalasti et al. (2019) found that subject pairs with higher ISC in certain cortical
21 regions during the stimulus ultimately shared more similar interpretations of the stimulus. These
22 studies provide a fascinating window into how individual differences in brain activity during
23 stimulus exposure relate to subsequent differences in reactions and interpretations. But because
24 both brain responses and behavior are tied to the specific stimulus at hand, the extent to which
25 these state-like differences reflect trait-like predispositions—i.e., intrinsic individual
26 characteristics—remains unclear.

27
28 Recent studies take these analyses one step further and link idiosyncratic responses during
29 naturalistic stimulation to stable, trait-like factors. Finn et al. (2018) report that individuals with
30 higher trait paranoia show stronger ISC in cortical regions involved in social processing during
31 an ambiguous social narrative. Bacha-Trams et al. (2018) report that individual differences in

cognitive style (i.e., holistic versus analytical thinking) relate to strength of ISC in several cortical regions during a drama movie. In a sample of college-age males, Chen et al (2019) report that variations in sociosexual desire preferences are linked to variations in brain activity in reward, default-mode and mentalizing networks, and self-control preferences to variations in executive and salience networks, during erotic (but not neutral) films. In a sample of children and adolescents spanning ages 7-21 years, Gruskin et al. (2019) report that patterns and severity of depression symptoms are linked to brain responses during an emotionally evocative animated clip, but only in adolescents, suggesting that these idiosyncratic responses emerge over the course of development. Finally, in a study of individuals with dyslexia, ISC calculated from MEG envelope time series correlated with similarity in phonological processing, technical reading, and working memory (Thiede et al., 2019). Encouragingly, these studies show that there is meaningful—i.e., behaviorally relevant—structure in idiosyncratic responses to naturalistic stimuli.

Other studies have addressed variability by dichotomizing subjects into diagnostic groups. Several studies have reported differences in ISC during naturalistic paradigms between healthy controls and populations with mental illnesses and disorders—most commonly, autism (Bolton et al., 2018; Byrge et al., 2015; Hasson et al., 2009; Salmi et al., 2013), but also depression (Guo et al., 2015) and first-episode psychosis (Mäntylä et al., 2018; Yang et al., 2019). In general, these studies report reduced cross-subject synchrony in the patient group, an effect that sometimes scales with symptom severity (Guo et al., 2015; Salmi et al., 2013).

Group contrasts between patients and controls can be useful to assess population-level differences in broad strokes. But rather than distinct canonical responses for each group, patients are typically characterized by increased heterogeneity of responses (Bolton et al., 2018). This suggests that a better framework would approach the question as an individual-differences problem. Indeed, Byrge et al.'s post-hoc analyses revealed that their ISC effect was driven entirely by five individuals from the ASD group with particularly idiosyncratic responses that could not be easily explained by other factors (i.e., data quality, symptom severity); when these five individuals were removed, the ASD and neurotypical groups were indistinguishable. Interestingly, Hasson et al. (2009) reported that while responses subjects with autism were more

variable, these idiosyncratic responses were reliable within single individuals across repeat presentations of the same stimulus, suggesting a trait-like component.

Rather than a dichotomy between health and disease, most mental illnesses are likely better conceptualized as the extreme end of a phenotypic spectrum (Cuthbert and Insel, 2013; Insel et al., 2010). Instead of stratifying subjects into patients and controls, we can improve sensitivity by using continuous measures—task performance, symptom severity, genetic load—as our independent variables (Finn and Constable, 2016). To then take advantage of the richness of information embedded in these continuous spaces, we need analysis frameworks that can appropriately handle the intricate interdependencies of dyads rather than individuals. Recent work has proposed using multilevel modeling and other expanded statistical formulations, some of which offer the ability to include subject-level covariates into ISC analyses (Chen et al., 2017). In the next section, we outline another promising approach, used by several of the studies cited above, that is flexible, intuitive and can be applied to detect relationships between any type of brain and behavioral data.

4. Inter-subject Representational Similarity Analysis: Theory

By definition, inter-subject correlation cannot be calculated for a single subject. How, then, can we relate ISC, which operates at the level of subject pairs, to traits and behaviors, which operate at the level of single subjects?

We can compute a similarity score between pairs of individuals using other types of data, for example self-report questionnaires, demographics, task performance, clinical assessments, or genotypes, among others. The intuition is that individuals who are more similar in behavior should also be more similar in their neural responses. We can operationalize this by computing two subject-by-subject distance matrices: one for the brain data (using, for example, ISC), and one for the behavioral data. We can then compare the geometry of these two matrices by

Figure 1. Schematic of inter-subject representational similarity analysis. Each subject (bottom layer) is associated with a behavioral score (middle layer) and a pattern of brain activity (top layer; in this case, a time series from a given brain region during naturalistic stimulation). In IS-RSA, we construct pairwise (i.e., subject-by-subject) similarity matrices for the behavioral data and the brain data, then compare these matrices using a Mantel test. Thus, we can leverage inter-subject analysis methods such as ISC to detect shared structure between brain data and behavioral data. This figure is a modified version of Fig. 1 in Gleason et al. (2016).

correlating them, a procedure known as a Mantel test (Mantel, 1967) or representational similarity analysis (Kriegeskorte et al., 2008). We and others call this inter-subject representational similarity analysis (Chen et al., 2019; van Baar et al., 2019). The advantage of comparing similarity matrices over a typical first-level analysis is that instead of directly linking two physically different quantities like brain data and behavior, we use a second-order isomorphism to compare the geometry of brain data with the geometry of behavioral data (Figure 1) (Kriegeskorte and Kievit, 2013).

This sounds straightforward enough. But one critical question is, how do we measure behavioral similarity? In choosing a distance metric, particularly when our behavior is one-dimensional (e.g., age (Moraczewski et al., 2018; Richardson et al., 2018), a trait score, accuracy on a cognitive task), we imbue our analysis with some fundamental assumptions about the structure of the brain-behavioral representational similarity that affect the ultimate results and how we interpret them. To get a feel for some potential structures, imagine arranging the rows and

1 columns of the ISC matrix such that subjects are ordered by their behavioral score. What would
2 we expect the resulting matrix to look like?
3
4 If we use Euclidean distance or another relative distance metric, we implicitly assume that
5 subjects with closer scores should look more similar to one another, regardless of where they fall
6 on the scale. In other words, for a behavior that is measured on a scale from 0 to 100, a pair of
7 subjects scoring 0 and 1 should be just as similar to one another as a pair of subjects scoring 99
8 and 100 (since in both cases, the Euclidean distance is 1). We call this the *Nearest Neighbors*
9 model, since it assumes that a subject should always look most similar to his or her immediate
10 neighbors, regardless of their absolute position on the scale (**Figure 2a**).

Figure 2. Simulated potential structures for brain-behavior representational similarity matrices. For each row a-d, the left panel depicts a simulated pairwise brain similarity matrix in which subjects are ordered along both rows i and columns j by their behavioral score (from low to high), and each cell $\{i, j\}$ reflects the correlation between subjects i and j of the timeseries of a given brain region (pairwise inter-subject correlation). The right panel depicts a two-dimensional embedding of the corresponding distance matrix (i.e., $1 - \text{similarity matrix}$) using t-SNE (t-Distributed Stochastic Neighbor Embedding), in which each dot represents a subject, and subjects are colored according to their behavioral score. Several potential structures are possible, including linear and non-linear relationships.

1

2 The NN model may be appropriate for certain behaviors, but we could imagine an equally if not

3 more plausible scenario: that similarity between subjects increases or decreases as one moves up

4 or down the scale, in an absolute rather than relative sense. For example, perhaps high-scoring

5 subjects are more similar to other high scorers, while low-scoring subjects are less similar both to

6 high scorers and other low scorers. In other words, brain responses cluster together for subjects

7 at one end of the behavioral spectrum, while variability increases as one moves toward the

opposite end of the spectrum. We call this the *Anna Karenina* (or *AnnaK*) model, after the famous opening line of Leo Tolstoy’s novel, which reads “All happy families are alike; each unhappy family is unhappy in its own way” (or, in this context, “all high [low] scorers are alike; each low [high] scorer is different in his or her own way”). In this case, Euclidean distance would not be the most appropriate choice. Instead, we would want to model similarity using a nonlinear metric that reflects absolute position—for example, mean: $(i + j)/2$, minimum: $\min(i, j)$, or the product of the mean and minimum (**Figure 2b-d**).

In the case of traits and behaviors that consist of a vector of responses per subject (e.g., self-report questionnaires) rather than a single scalar number (e.g., age), we have the option to calculate item-wise similarity using any number of potential distance metrics—for example, correlation, Euclidean distance, cosine distance and many others. In this case, we are assuming that it is the pattern of individual responses, and not the composite score, that should determine the inter-subject similarity structure. This approach is likely best suited to assessments consisting of unique items that are not interchangeable—personality questionnaires, for example¹. As a general heuristic, quantitative assessments—those with clear “better” and “worse” ends of the scale—are likely more suited to distance models based on single composite scores, while qualitative scales could be suited to either composite or item-wise models. We can also imagine scenarios where both models are theoretically appropriate, and each might capture different effects. For example, questionnaires assessing symptom type and severity might show some effects that scale with overall score (*Anna Karenina* model), and others that scale with item-wise similarity (nearest neighbors)—and each of these effects might be present in different brain regions.

5. Inter-subject RSA: Application to HCP data

To investigate if and how brain similarity reflects behavioral similarity during naturalistic stimulation, and more specifically, how the choice of distance model affects results, we applied

¹ Since most cognitive performance tests consist of more than one item, we could in theory calculate item-wise distance on these tests as well. But because trials in these tests are generally interchangeable, it is more straightforward and interpretable to consider the similarity of two subjects’ composite score rather than the similarity of their performance on individual trials (unless one has a specific hypothesis about learning rates, attention fluctuations, or other effects with a dynamic component).

inter-subject RSA to an empirical dataset from the Human Connectome Project. Subjects engaged in a movie-watching paradigm during high-resolution (voxel size = 1.6mm^3 , TR = 1s) functional MRI scanning at 7 Tesla. The sample used here ($n = 184$, from 93 unique families) reflects all available data for this paradigm. Details of data acquisition and basic preprocessing are published elsewhere (Glasser et al., 2013; Van Essen et al., 2012; Vu et al., 2017). Each subject watched four 15-minute movie runs; data from the first run (MOVIE1_7T_AP) are used here. This run comprised five video clips presented in a fixed order. Four clips were from independent films and documentaries, and one was a montage of brief (1.5s) moving scenes.

Each subject also completed a battery of self-report and behavioral measures outside the scanner (Barch et al., 2013). We focused on two trait-level measures from the cognitive and emotional domains, respectively: working memory (as measured by a list-sorting task) and personality (as measured by the NEO Five-Factor Inventory). We chose these two traits because we hypothesized that the structure of brain-behavior similarity would manifest differently for each one, and therefore that each trait would be best modeled by a different distance function in IS-RSA, as detailed below.

The primary outcome measure from the list-sorting task is a measure of working memory span, or how many items can be accurately stored and manipulated in working memory at one time. Because it yields a single scalar score per subject, behavioral similarity can be computed according to either a nearest-neighbors or AnnaK model. The NEO-FFI consists of 60 items, and subsets of these are summed to yield scores for five dimensions: agreeableness, extraversion, conscientiousness, neuroticism, and openness. Therefore, for personality, we can compute behavioral similarity in any of three ways: (1) AnnaK for each of the five traits (to test the prediction, e.g., that people who are more agreeable share similar patterns of brain activity, while people that are less agreeable show more variability); (2) nearest-neighbors for each of the five traits (people that score more similarly on agreeableness look more similar, regardless of whether they score high or low); or (3) nearest-neighbors for all 60 item-wise responses (people who fill out the questionnaire in more similar ways, regardless of their summary trait scores, will show more similar brain activity). We tested all possible models for each behavior (two for working memory and three for personality). We hypothesized that working memory would be best

1 captured by an AnnaK model in most brain regions. We did not have strong hypotheses about the
2 best model for personality, as any of the above scenarios were plausible *a priori*.

3
4 Because we might expect both behavioral phenotypes and brain activity to be more similar
5 between siblings—and especially twins—due to any number of genetic and environmental
6 influences, we avoided performing IS-RSA on related individuals. We split the dataset into two
7 cohorts of unrelated subjects ($n = 93$ and $n = 89$, respectively), which had the benefit of giving us
8 a natural replication sample to help guard against false positives. We performed all analyses on
9 each cohort separately, and only relationships that appeared in both cohorts were considered
10 “significant”.

11
12 Beginning with the FIX-denoised data, for each subject, we extracted activity timecourses from
13 every node in a 268-node functional parcellation (Shen atlas; (Shen et al., 2013)) by averaging
14 signal across all voxels for each volume. (Because activity is expected to be smooth across
15 neighboring voxels, this step reduces the dimensionality of the data, thus avoiding the
16 computational cost of a voxelwise analysis.) For each node n and each subject pair $\{i, j\}$ within a
17 cohort, brain similarity was calculated as the Pearson correlation (ISC) across the whole run.
18 Behavioral similarity was calculated according to either an NN model ($i - j$; **Figure 2a**) or an
19 AnnaK model ($\text{mean}(i, j)$; **Figure 2b**).

Working Memory

Figure 3. Inter-subject RSA applied to HCP data: Working Memory. Do pairs of subjects that score more similarly on a test of working memory (HCP: ListSort) also show stronger ISC in certain brain regions during naturalistic viewing? Two models for behavioral similarity are tested: a nearest-neighbor model (top row; cf. **Figure 2a**) where the behavioral similarity matrix is constructed as $|i - j|$, and an “Anna Karenina” model (bottom row, cf. **Figure 2b**) where the behavioral similarity matrix is constructed as $\text{mean}(i, j)$. In the scatter plots, each dot represents one node in the Shen atlas (268 total), plotted according to its representational similarity (Spearman correlation between brain similarity and behavioral similarity matrix) in cohort 1 (x-axis) versus its representational similarity in cohort 2 (y-axis). Large black dots are nodes that show significant representational similarity ($p < 0.05$) after permutation testing (no. permutations = 10,000) in both cohorts. Dashed lines along the diagonal represent the identity line (not the regression line), to facilitate visual inspection of replicability—ideally, the RSA values would be similarly distributed in cohort 1 and cohort 2, and the correlation between the two cohorts would be close to 1. Glass brains show nodes colored by is-RSA value. Nodes outlined in black show significant representational similarity in both cohorts (corresponding to the large black dots in the scatterplots).

- 1 For working memory, as we hypothesized, representational similarity between brain and
- 2 behavior was best captured by the AnnaK model (**Figure 3**, bottom row). High-scoring subjects
- 3 looked similar to other high scorers across much of the brain, while low-scoring subjects had
- 4 more idiosyncratic responses—in other words, they looked less similar to both the high scorers
- 5 and other low scorers. The AnnaK model fit the data better than the nearest-neighbors model in
- 6 that it yielded stronger effect sizes (compare distributions of RSA values between the two scatter
- 7 plots in **Figure 3**) that were more replicable across the two subject cohorts ($r_{\text{cohort 1, cohort 2}} = 0.60$
- 8 for the AnnaK model versus 0.18 for the NN model). The AnnaK model captured significant
- 9 relationships between brain and behavioral similarity in 53 nodes across parietal, temporal,

1 occipital and cerebellar cortex, while the nearest-neighbors model detected a relationship in only
2 two nodes.
3

a. Personality: Itemwise

b. Personality: Trait scores

Figure 4. Inter-subject RSA applied to HCP data: Personality. Do pairs of subjects with more similar personalities (as measured with the Five-Factor Inventory) also show stronger ISC in certain brain regions during naturalistic viewing? a) IS-RSA, where personality similarity is calculated as the Pearson correlation between item-wise responses of each pair of subjects (“NN-itemwise”). b) IS-RSA where personality similarity is calculated based on summary scores for each of the five traits. For each trait, two models for behavioral similarity are tested: a nearest-neighbor model (top graph in each column; cf. **Figure 2a**) where the behavioral similarity matrix is constructed as $|i - j|$, and an “Anna Karenina” model (bottom graph in each column, cf. **Figure 2b**) where the behavioral similarity matrix is constructed as $\text{mean}(i, j)$. In all scatter plots, each dot represents one node in the Shen atlas (268 total), plotted according to its representational similarity (Spearman correlation between brain similarity and behavioral similarity matrix) in cohort 1 (x-axis) versus its representational similarity in cohort 2 (y-axis). Large black dots are nodes that show significant representational similarity ($p < 0.05$) after permutation testing in both cohorts. Dashed lines along the diagonal represent the identity line (not the regression line), to facilitate visual inspection of replicability—ideally, the RSA values would be similarly distributed in cohort 1 and cohort 2, and the correlation between the two cohorts would be close to 1. Nodes outlined in black on show significant representational similarity in both cohorts (same as those in the scatterplots). Traits with no corresponding glass brain figure did not have any nodes that were significant in both cohorts (“n.s.”).

For personality, results were more complicated. Using trait summary scores, the nearest-neighbor model based on trait summary scores did not yield any significant nodes across any of the five dimensions (**Figure 4b**, top scatter plots), and the AnnaK model yielded only two significant nodes across all five dimensions (**Figure 4b**, bottom scatter plots): one in the left middle temporal lobe that showed higher ISC among pairs of subjects scoring low on conscientiousness (**Figure 4b**, glass brain), and one in the orbitofrontal cortex that showed higher ISC among pairs of subjects scoring high on openness (**Figure 4b**, glass brain). However, the nearest-neighbor model based on item-wise responses captured several (16) nodes across the brain (**Figure 4a**), including fusiform, right inferior frontal gyrus, and several nodes in the cerebellum. Interestingly, this suggests that brain responses during naturalistic stimulation may depend less on overall levels of certain personality traits, and more on personality “fingerprints” captured by specific patterns of item-wise responses to the personality questionnaire.

In sum, we observed that different traits and behaviors are best modeled by different distance functions in different brain regions. These results raise several questions to be addressed in future work. For example, which model(s) perform best on other traits and behaviors? Can we use dynamic analyses (Glerean et al., 2012; Simony et al., 2016) to reveal particular time windows where the brain-behavior signal is strongest? Do these windows relate to known features of the stimulus? For now, we can conclude that IS-RSA is a promising framework to detect brain-behavior relationships during naturalistic imaging, and that choosing the appropriate model not only improves sensitivity, but also offers the flexibility to test multiple hypotheses with fundamentally different interpretations.

6. Inter-subject RSA: Future directions

Extending IS-RSA to a predictive framework

So far, we have discussed inter-subject RSA as a way to relate brain similarity to behavioral similarity in a fixed set of subjects. Eventually, however, we would like to build models that can generate predictions about never-before-seen individuals (Bzdok and Ioannidis, 2019; Gabrieli et al., 2015). How might we extend IS-RSA to a predictive framework?

1 In many cases, we might want to build a decoding model, which uses a subject's pattern of brain
2 activity during naturalistic stimulation to generate a predicted behavioral score for that subject.
3 The *AnnaK* models predict a monotonic relationship between a subject's behavioral score and
4 their mean (or median) ISC value with all other subjects. Therefore, a simple model might
5 parameterize this relationship in a set of training subjects, then calculate the mean ISC for a held-
6 out subject with all subjects in the training set and input this value into the model to generate a
7 predicted behavior. Alternatively, one could build a model based on a "canonical" timecourse
8 calculated from high (or low) scorers in the training set and generate a predicted score for a held-
9 out subject based on their distance from this canonical timecourse.

10
11 The NN models do not predict any relationship between behavior and overall mean or median
12 ISC value, but rather between behavior and ISC with specific partners. To translate this to a
13 predictive model, we could use a k -nearest neighbors framework that would predict a held-out
14 subject's behavioral score as a weighted average of scores from the k subjects in the training set
15 with whom they show the highest ISC.

16
17 In either case, certain brain regions would likely show a stronger relationship between ISC and
18 behavior than other regions. Feature selection could be applied to uncover the brain regions
19 where similarity is most strongly related to behavioral similarity, to improve model performance.

20
21 Alternatively, we could invert this framework to build *encoding* models, which, given a stimulus
22 and a behavioral score, predict a subject's timecourse of brain activity. While this may prove
23 more difficult, a successful model would provide a mapping for how an intrinsic trait and a
24 complex stimulus interact to produce activity in a given brain region (Naselaris et al., 2011), a
25 powerful step forward in understanding how complex stimuli are filtered through an individual
26 lens.

27 *Unsupervised IS-RSA*

28
29 As we amass larger datasets that include naturalistic neuroimaging, it may become possible to
30 perform unsupervised analyses. In other words, instead of using known behavioral scores to pre-
31 label the data, we could cluster inter-subject brain similarity matrices to detect natural categories

or continua in a data-driven fashion, then see if these relate to present or future behavioral outcomes (Cerliani et al., 2017). In this way, we may be able to leverage naturalistic neuroimaging to organize individuals along axes that are more biologically valid than current diagnostic and self-report measures, potentially shedding new light on how individual variability is reflected in nuanced brain function.

More sophisticated temporal techniques

Thus far we have been using inter-subject correlation, or simple Pearson correlation between two subjects' timeseries, as our primary measure of brain similarity, largely because it is straightforward to compute, visualize, and interpret. However, in theory we could calculate a brain similarity matrix (cf. **Figure 1**) based on any type of information we might extract from single subjects' neuroimaging data. For example, we could use functional connectivity (Glerean et al., 2016), or compare subjects' temporal trajectories over the course of a stimulus using low-dimensional topological embeddings (e.g., (Gonzalez-Castillo et al., 2019; Saggar et al., 2018)), latent state discovery (Chang et al., 2018), or projection into a higher-order space using recurrent neural networks (Venkatesh et al., 2019). Furthermore, the brain and behavioral inter-subject similarity matrices (cf. **Figure 1**) can be also interpreted as networks. This approach allows for more robust measures of similarities between two networks without the strong dependence on the actual link weights and even allows for missing data points between subject pairs (Peixoto, 2015; Schmidt and Morup, 2013). These approaches may prove even more powerful for uncovering brain-behavior relationships during naturalistic imaging, though potentially at the expense of some interpretability.

7. Stimulus selection: How much synchrony is enough?

Thus far, we have discussed how to optimize sensitivity to stimulus-evoked individual differences from an analysis perspective. What about from an acquisition perspective? While naturalistic imaging experiments are growing in popularity, currently, there is no principled way to choose stimuli. Common wisdom is that for studying shared responses, we should choose something maximally engaging, to “drive” as much of the brain as possible. Indeed, previous work has shown that features of the stimulus affect ISC levels: more rhetorically powerful speeches (Schmälzle et al., 2015), emotionally arousing narratives (Nummenmaa et al., 2014),

1 and highly rated television programs (Dmochowski et al., 2014) all evoke higher synchrony than
2 their less engaging counterparts.

3
4 But, when the goal of a study is specifically to investigate individual differences, considerations
5 for choosing a stimulus may be different. In the theoretical limit, a stimulus that evoked perfect
6 synchrony across subjects would be useless for studying individual differences—since there
7 would be no neural variability to relate to behavioral variability (Hedge et al., 2018). Practically,
8 however, we are quite far from that theoretical limit, since individual BOLD responses are
9 “noisy” both in terms of uninteresting variability (scanner noise, non-neural BOLD signals,
10 stimulus-unrelated neural activity) and the stimulus-driven idiosyncratic responses that constitute
11 the “signal” of interest here.

12
13 Is there a “sweet spot” where a stimulus evokes enough synchrony to build a successful cross-
14 subject model, but not enough to saturate the individual signals of interest? To test their
15 hypothesis that social network proximity predicts increasingly similar neural responses to
16 movies, Parkinson et al. (2018) chose videos that might differentially appeal to those with
17 different tastes (reasoning that friends would be more likely to have similar tastes; e.g., styles of
18 humor, opinions on controversial topics). A handful of studies have created bespoke stimuli that
19 were ambiguous by design, such that different individuals might arrive at different
20 interpretations of the same material. Finn et al (2018) created a narrative describing a complex
21 social scenario that seemed highly suspicious or nefarious to some individuals, but less so to
22 others; Nguyen et al (2018) created a Heider-Simmel-esque video (Heider and Simmel, 1944)
23 depicting an interaction among animated shapes in which the relationships between the shapes
24 were open to interpretation. These studies found that individuals who were more similar on
25 either trait-level (i.e., intrinsic) or state-level (i.e., stimulus-driven) measures, respectively,
26 showed increased inter-subject correlation during stimulus presentation in regions of higher-
27 order association cortices, especially those linked to social cognition.

28
29 None of these studies, however, directly assessed how the level of ambiguity or so-called “taste-
30 dependence” of a stimulus affects its utility for drawing out meaningful individual signal. If the
31 goal is to study idiosyncratic responses, how much synchrony is optimal? If we imagine plotting

stimuli by the strength of the ISCs they evoke versus their sensitivity to individual differences, several potential scenarios emerge (**Figure 5.**). In theory, idiosyncratic signals might be quickly saturated by a powerful stimulus, such that the optimal stimulus would evoke only minimally correlated responses when averaged across all subjects, leaving room for specific subject pairs to be more or less correlated with one another according to variations in behavior (Scenario 1). Alternatively, the optimal level of average synchrony could be higher, such that sensitivity to individual differences benefits from a stronger foundational shared response at the group level (Scenario 2). Another possibility is that the theoretical “saturation point” is much higher, such that stimuli that evoke very strong responses are the ones that are most sensitive to individual differences (Scenario 3). This third scenario would be consistent with the observation that stimuli and task states that make subjects look more similar to one another can actually boost signal-to-noise for individual differences, since even though these states reduce overall cross-subject variation, the remaining variation is presumably more stable and trait-like (Finn et al., 2017; Vanderwal et al., 2017).

Figure 5. Theoretical stimulus tuning curves for sensitivity to individual differences. In the upper limit, as the degree of cross-subject synchrony evoked by a stimulus approaches 1, that stimulus will lose sensitivity to individual differences, since there will be no brain variability left to relate to behavioral variability. However, in the lower limit, if a stimulus evokes no correlation across subject, there will be no meaningful structure in brain similarity to relate to behavioral similarity. Therefore, the optimal tuning curve likely follow an inverted-U shape. Determining the peak of this curve—in other words, the optimal degree of synchrony for extracting meaningful individual differences in a certain behavioral domain—should be a goal for future work.

Understanding how stimulus choice affects sensitivity to individual differences will be an important area for future research, especially as large-scale data collection efforts begin to incorporate naturalistic scans into their protocols (Alexander et al., 2017; Van Essen et al., 2012). We believe acquiring naturalistic scans should be encouraged for several reasons: beyond improving subject compliance (and therefore data quality) compared to resting-state scans (Greene et al., 2018; Huijbers et al., 2017; Vanderwal et al., 2015), naturalistic paradigms yield data that can be mined in any number of ways, expanding their potential to generate insights into a variety of open questions in human

neuroscience. Yet, to the extent that stimulus choice affects the individual signals we observe, it will behoove us to be as principled as possible in choosing stimuli.

Of course, there may not be a single “best” stimulus for studying individual differences; rather, the most appropriate stimulus may depend on the specific behavior(s) of interest. For example, a threatening or suspenseful stimulus—e.g., the opening scene in a horror film—might evince neural responses that share structure with trait anxiety, as compared to one depicting positive emotion—e.g., the happily-ever-after final scene of a romantic comedy. Conversely, the positive stimulus might yield better predictions of trait anhedonia. At the same time, both of these stimuli may yield better predictions of either trait than a neutral stimulus with little to no emotional content. Testing these hypotheses will require datasets with a range of both stimuli and behavioral measures per subject. However, there is already some supporting evidence: for example, differences between controls and patients with melancholic depression are more pronounced during a negative film clip than a positive one (Guo et al., 2015).

8. Limitations

Despite the many clear advantages and—we believe—great potential of using naturalistic paradigms to study individual differences, there are several outstanding challenges. For one, the test-retest validity of these paradigms is unclear. Repetition is known to alter neural processing, and this is likely especially true for emotionally evocative and memorable stimuli. Thus, naturalistic paradigms that rely on a single stimulus may be less appropriate for longitudinal studies, since it would be near impossible to disentangle within-subject changes from repetition effects.

There are computational challenges associated with using inter-subject approaches, since pairwise techniques mean that the number of observations increases as n^2 rather than n . Especially in the case of ISFC, reducing dimensionality using pre-defined atlases, and/or selecting regions of interest based on *a priori* hypotheses or a first-pass analysis of which regions surpass some minimal threshold for response consistency (cf. **Figure 5.**), may help in this regard.

Another challenge, albeit not one unique to naturalistic paradigms, is understanding which traits and behaviors we should target. Predicting a performance-based or self-report measure acquired close in time to the imaging data itself, which is the goal of the vast majority of the current literature on brain-behavior relationships, is an important proof-of-concept, but ultimately the imaging data will always be simply a noisier version of whatever “ground truth” we are trying to predict. Determining the added value of neuroimaging will require using baseline brain responses to naturalistic stimuli to predict follow-up measures such as learning rates (Cantlon and Li, 2013), illness trajectory, or response to intervention.

9. Concluding remarks

Here, we have advanced an emerging framework for studying individual differences during naturalistic neuroimaging, a phenomenon we call “idiosynchrony”. Inter-subject representational similarity analysis (IS-RSA) combines the time-locked nature of the stimulus with known phenotypic information to move from shared responses to activity in individual subjects that is idiosyncratic, yet structured and interpretable. Unlike traditional approaches that rely on explicit models of the task, inter-subject approaches promise to capture as much nuance and variance of the evoked activity as possible. And, unlike functional connectivity approaches that treat naturalistic neuroimaging data akin to rest, inter-subject approaches afford near certainty that the observed signals are both neural in origin and driven by the stimulus. Above and beyond a boost in signal-to-noise, these paradigms open up exciting opportunities to link individual patterns of brain activity to specific events within the stimulus that unfold over various timescales, from its low-level sensory properties up to high-level narrative features that may evoke different memories, associations and emotions for each individual. Linking naturalistic patterns of brain activity to trait- and state-related variability across subjects will deepen our understanding of how individual brains give rise to individual behaviors, and may eventually help empower imaging-based tools for real-world applications.

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Data and code availability

Raw data for the empirical results presented here come from the Human Connectome Project (<http://www.humanconnectomeproject.org/>). Code for all IS-RSA analyses—both simulations (cf. **Figure 2**) and empirical application to HCP data (cf. **Figure 3**, **Figure 4**)—can be found in the following Github repository: https://github.com/esfinn/intersubj_rsa, which also contains the processed HCP data (nodewise time series) that formed the input to the empirical analyses.

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