**Subject- and behavior-specific signatures extracted from fMRI data using whole-brain effective connectivity**

AUTHORS:

Pallares V\*1, Insabato A\*1,2, Sanjuán A1, Kühn S3,4, Mantini D5,6,7, Deco G\*\*1,8, Gilson M\*\* 1

\* Equal contribution

\*\* Equal contribution

1. Center for Brain and Cognition, Computational Neuroscience Group, Department of Information and Communication Technologies, Universitat Pompeu Fabra, Carrer de Ramon Trias Fargas, 25-27, Barcelona, 08005, Spain

2. The Italian Academy, Center for Theoretical Neuroscience, Columbia University, 1161 Amsterdam Ave., New York NY 10027, USA

3. Max Planck Institute for Human Development, Center for Lifespan Psychology, Lentzeallee 94, 14195 Berlin, Germany

4. University Clinic Hamburg-Eppendorf, Clinic and Policlinic for Psychiatry and Psychotherapy, Martinistraße 52, 20246 Hamburg, Germany

5. Research Center for Motor Control and Neuroplasticity, KU Leuven, 101 Tervuursevest, 3001 Leuven, Belgium

6. Department of Health Sciences and Technology, ETH Zurich, Winterthurerstrasse 190, 8057 Zurich, Switzerland

7. Department of Experimental Psychology, Oxford University, 15 Parks Road, Oxford OX1 3PH, United Kingdom

8. Institució Catalana de la Recerca i Estudis Avanats (ICREA), Universitat Pompeu Fabra, Passeig Lluı́s Companys 23, Barcelona, 08010, Spain

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**INTRODUCTION**

Blood-oxygen-level dependent (BOLD) signals in functional magnetic resonance imaging (fMRI) have been used for more than two decades to observe human brain activity and relate it to functions [1,7]. The context of the present study is about robustly extracting behavioral and individual information from fMRI data. Even at rest, the brain exhibits patterns of correlated activity between distant areas [4,39]. The functional connectivity (FC) measures the statistical dependencies between the BOLD activities of brain regions, which has then been studied for subjects performing tasks and compared with the resting state [xxxError: Reference source not found]. Recent interest has focused on the temporal BOLD structure: using the frequency spectrum of individual regions [28], measuring the cross-covariance lags (at the scale of seconds) between areas [36] and ‘dynamic FC’ to quantify the BOLD correlations at the scale of minutes [24]. Following fundamental discoveries about brain functions, fMRI has been increasingly used to complement clinical diagnostic for neuropathologies [34]. Resting-state fMRI has also been found to be informative about neuropsychiatric disorders [26]: alterations in FC correlate with and can predict the clinical scores of several diseases [31,40].

Recent studies have focused on the reliability of these FC measures recorded from the same subject over successive sessions [43,37,6,38]. Consistent differences between subjects (with individual stability) allow subject identification using recorded FC as a “fingerprint” [15]. Moreover, this subject specificity may even be enhanced in task-evoked activity [16]. Another model-based approach used linear-regression coefficients of BOLD signals instead of FC to identify the subjects [35]. A recent prospective study about the evolution of psychiatric disorders emphasized individual specificities in the FC stabilization during childhood (irrespective of the disease) [33], whereas traditional group-averaging aims to remove the individual differences to obtain task-specific [48] or pathology-specific [11] signatures. The mixture of session-to-session, subject-specific and condition-related variability in FC is a crucial issue for real-life applications where only a few sessions per subject can be recorded, such as clinical diagnostic. Because previous studies [15,35,16] were limited to datasets with at most 3 resting-state sessions per subject, we aim to rigorously assess the generalization capability of prediction methods to future (unseen) data.

Distributed signatures in FC across the whole brain have been observed in memory tasks [41] or when the subject experiences psychological pain [5]. Moreover, the etiology of many mental disorders is unknown: they are suspected to arise from network dysfunction, as reported for large-scale FC alterations in patients with schizophrenia [32]. These examples strongly point in favor of whole-brain approaches to study high-level cognition [9] and brain diseases [10]; in contrast, focusing on a few cortical areas only to test hypotheses [23,2] may not capture sufficient information and network effects. Xxx However, such whole brain approaches typically involve a large number of parameters to estimate, which may impair the robustness. One of the aim of the present study is to bring a practical answer to this trade-off dilemma.

The idea underlying the study of FC – in the broad sense – lies in that it reflects how brain areas dynamically bind to exchange and process information [18,29,3]. To move beyond a phenomenological description of FC, our method relies on a model inversion [21] to interpret FC by decomposing it into changes in network connectivity and local fluctuating activity. Note that we borrow the terminology of effective connectivity (EC) to describe the interactions between brain regions from dynamic causal model [19], although our model implies simplifications in comparison. As with FC, a crucial issue for EC is whether the estimated model parameters are reliable across several sessions for the same subject [17], which determines whether they can predict the subjects' identities in practice [35].

The present study aims to set a new standard to extract multivariate signatures from fMRI data, discriminative against subjects or behavioral conditions. The paper is organized in two parts. First, we couple whole-brain EC estimation with adequate machine learning tools to identify subjects from resting state fMRI (i.e., classify single sessions to the corresponding participant) capitalizing on previous studies [15,35]. The focus is on the comparison between EC and FC in their generalization capabilities. To do so, we rely on datasets with large numbers of sessions and healthy subjects to control the effect of session-to-session variability. Second, we predict both the subject's identity and condition (rest versus movie viewing) to verify that EC can disentangle the two types of signatures. Doing so, we examine the topological distribution of the EC links supporting the twofold classification. Although we test the method on behavioral conditions, we benchmark it keeping in mind future applications to clinical diagnostic.

**RESULTS**

In this study we used fMRI data from three datasets:

- The first dataset, from the Day2day study, was acquired at the Max Planck Institute for Human Development in Berlin for two different resting-state studies [14]: 6 subjects were scanned 40-50 times over six months with 5-minute sessions (Dataset A1); 50 participants underwent a single session in the same scanner (Dataset A2). This dataset was used to test the robustness of subject identification to session-to-session variability.

- Dataset B has been made publicly available by the Consortium for Reliability and Reproducibility [50] and contains resting-state fMRI sessions from 30 participants. Each subject underwent 10 times a 10-minute scanning session every three days for one month. This dataset was used to test the generalization capability of the identification procedure for a larger number of subjects than Dataset A.

- Dataset C includes 22 subjects with 5 sessions of 10 minutes each in two different conditions, two sessions at rest and three sessions watching a movie [22]. This dataset was used to obtain both individualized and behavioral signatures, irrespective of the between-session variability.

After applying a standard preprocessing pipeline to the BOLD signals (see Methods for details), we parcellated the brain into 116 regions of interest (ROIs) by using a standard anatomical space [46] for Datasets A1, A2 and B (see Figure 1A). Dataset C was parcellated into 66 ROIs covering the cortex [27].

**Functional and effective connectivity as measures of the brain network dynamics**

Classical functional connectivity (corrFC) was calculated using the pairwise Pearson correlation coefficient (PCC) between the ROI time courses, obtaining an mxm symmetric matrix for each recorded session (m=116 for Datasets A and B, m=66 for Dataset C); see Eq. 2 in Methods. In addition, we used a whole-brain dynamic model [21] (Figure 1B): each ROI is a node in a noise-diffusion network whose topology (skeleton) is determined by the structural connectivity (SC) obtained from diffusion tensor imaging (DTI) or similar techniques. In the model, the global pattern of FC arises from the local variability Σi that propagates via the network connections ECij (from j to i). To fit each fMRI session, all relevant ECij and Σi parameters are iteratively tuned such that the model spatio-temporal FC – as measured by FC0 (0-lag covariances) and FC1 (1-lag shifted covariances) – best reproduces the empirical counterpart. A detailed description of the model and the maximum-likelihood estimation procedure is provided in Methods. In essence, the model inversion decomposes the empirical matrices (FC0,FC1) into two estimates EC and Σ, which can be seen as multivariate biomarkers for the brain dynamics in each fMRI session.

**FIGURE 1**

**Similarity of connectivity measures across sessions and subjects**

Using Datasets A and B, we compared the capability of the 4 connectivity measures (corrFC, FC0, FC1 and EC), as well as Σ, in terms of within- and between-subject similarity (WSS and BSS, respectively), as a first step toward subject identification. For each pair of sessions, the similarity SX was calculated using the PCC between two z-scored vectorized connectivity measures X (non-zero elements for EC, low-triangle elements for corrFC; see Figure 1C, Eqs. 12 and 13 in Methods). In the matrix of SEC values for Dataset A1 (Figure 2A), 6 diagonal blocks with larger values corresponding to the WSS can be noticed; the remaining matrix elements correspond to BSS. Figure 2B compares the distributions of SEC and ScorrFC: WSS and BSS distributions are better separated for EC than for corrFC. In other words, sessions from the same subject are more similar to one another, and more different from those of other subjects, viewed from the EC than the corrFC viewpoint. This suggests a better capability of EC to discriminate between subjects. Note that the BSS from Datasets A1 (6 subjects) and A2 (50 subjects) remarkably overlap for both corrFC and EC, showing that BSS of 6 subjects generalizes well to larger number of subjects.

These qualitative observations are confirmed by the Kolmogorov-Smirnov (KS) distance between similarity distributions (blue versus red and blue versus green in Figure 2B). As summarized in Table 1, EC gave larger KS distance than corrFC and all other FC-related measures. Note that we also calculated KS distance using only the links in corrFC and FC0 corresponding to the 4056 existing connections in EC (determined by SC), in order to compensate for the (relative) sparsity of EC links as compared to corrFC and FC0; this did not change the results. Last, the diagonal elements of Σ showed the smallest distances. In the remainder of the article we focus on connectivity measures (EC and corrFC). Supplementary Figures S1 and S2 show the similarity distributions for FC0, FC1, corrFC/SC and Σ using Datasets A1 and B.

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | Dataset A1 | Dataset A1 & A2 |
| EC | EC weights estimated with the model | 0.6440 | 0.6581 |
| corrFC | FC computed as Pearson correlation | 0.4517 | 0.5477 |
| FC0 | FC computed as 0-lag covariance matrix | 0.3685 | 0.4888 |
| FC1 | FC computed as 1-lag covariance matrix | 0.4139 | 0.5118 |
| corrFC/SC | FC computed as Pearson correlation and masked with SC | 0.4769 | 0.5729 |
| FC0/SC | FC computed as 0-lag covariance matrix and masked with SC | 0.3770 | 0.4644 |
| Σ | Local variability for each ROI estimated with the model | 0.3778 | 0.3287 |

**Table 1.** Kolmogorov-Smirnov (KS) distance between WSS and BSS distributions for connectivity measures (corrFC, FC0, FC1) and model estimates (EC, Σ). The third column corresponds to the distance between the blue and red distributions in Figure 2B, and the fourth column to the blue and green distributions.

**FIGURE 2**

**Structure of individual session-to-session variability for EC and corrFC**

The high dimensionality of our connectivity measures may reduce their predictive power, known as Hughes phenomenon [30]. This is especially important in our case where the number p of dimensions for the multivariate measures (Dataset A1: p=4056 for EC, p=6670 for corrFC) exceeds the number n of samples (n=6 subjects x 50 sessions=300 samples). To further characterize individual variability over sessions, we performed a reduction of dimensionality using principal component analysis (PCA) on the sessions of Dataset A1. By the naked eye, the colored clouds representing all sessions for each subject exhibit smaller overlap for EC than corrFC (Figure 2C), where data are projected onto the first 6 principal components (PCs).

We quantified the clustering degree of these clouds using a silhouette coefficient for each session (see Eq. 16 in Methods), ranging from -1 (poor clustering) to 1 (perfect clustering). As shown in Figure 2D, EC produced larger (almost all positive) silhouette values than corrFC, confirming the visual impression of Figure 2C. Silhouette coefficients were calculated on the data projected onto the first 6 PCs, i.e. the number of PCs that maximized the silhouette coefficient (see Figure S3). As can be seen in Figure 2E, the silhouette coefficients for the data in the original link space (left violin plots) are smaller than those for data in the PCs space (right), for both datasets (Dataset B: first 27 PCs are used, for which the silhouette is maximized, see Figure S3). Consequently, PCA facilitate the identification of subjects by reducing the dimensionality of the data.

**Subject identification using EC is more robust than using corrFC**

Now we turn to the main goal of our study: the classification of single sessions – attributing them to subjects – based on EC or corrFC. Robust subject identification was pioneered by a recent publication [15] for more than 100 subjects, relying on a k-nearest-neighbor (kNN) classifier with k=1 and PCC as metric (see Methods for details). In order to classify a *target* session, the PCC between the target and 1 known reference session for each subject *(*called *database*) is calculated; the predicted identity for the target is that of the subject corresponding to the closest (most similar) session (see Figure S4). In contrast with previous studies using 1NN [15,16,33], our method relies on multinomial logistic regression (MLR) classifier, a classical tool in machine learning. MLR uses a linear model to predict the probability that an input sample belongs to a class (subject here). A technical comparison of both approaches is further detailed in Methods.

In classification algorithms the problem of overfitting describes the situation where the algorithm performs very well with the data it is trained with, but fails to generalize to new samples. Due to the high dimensionality of the connectivity measures [30], it is essential to control for overfitting with an appropriate training and test procedure. Our train-test procedure and the use of large test-retest datasets – unlike previous studies [15,16,47] – aims to provide a trustworthy characterization of the quality of the classifiers. Figure 3A describes the train-test procedure for the identification of subjects: 1) fMRI sessions (EC in the figure) are randomly split in training and test datasets; 2) after preprocessing (orange arrows) involving within-session z-score followed – or not – by PCA, the classifier is optimized as illustrated for the MLR with boundaries that best predict the training dataset; 3) test set is used to verify the generalization capability of the classifier (blue arrows), by measuring to which extent the classifier boundaries, estimated with the training set, correctly classify single sessions from the test set.

We first used Dataset A1: we increased the number of training sessions per subject from 1 to 40 to evaluate how many training sessions are necessary for satisfactory accuracy. As shown in Figure 3B, EC (in red) outperformed corrFC (in blue) by more than one standard deviation (shaded area around the curve), for both MLR and 1NN. Moreover, almost perfect classification was reached with MLR for 5 training sessions only, whereas 10-15 were necessary for 1NN. Figure 3C displays the classification accuracy on Dataset B , used to test the robustness of the algorithms with respect to the number of subjects to be classified. We trained the algorithms with 1 session per subject and evaluated the classification performance varying the number of subjects from 2 to 30 (test set comprised the remaining 9 sessions per subject). Again, EC is more robust than corrFC: while performance with corrFC rapidly deteriorates as the number of subjects is increased, classification using EC is barely affected by the number of subjects. Also with this dataset MLR confirms its superiority to 1NN. These results show that EC and MLR allow better performance than corrFC and 1NN; importantly, the performance is especially improved between 1 and 10 training sessions per subject, which is the interesting range for (clinical) applications.

Contrary to the analysis of the data structure (Figure 2E), PCA only marginally increases the performance when only 1 session is used with MLR and EC for Dataset A1 (less than 1% of difference between means, see Figure S5). The performance increase is slightly larger (~3%) with 1NN and EC: 1NN benefited more from the data denoising because it achieved a lower accuracy compared to MLR. Two factors limit improvements by PCA: 1) the classification accuracy is already very high with ~95% for MLR and EC with 1 training session; 2) EC is much less noisy than corrFC (see Figure 2B). PCA also allows for the investigation of the distribution of the subject-discriminative information between PCs. As shown in Supplementary Figures S6, S7 and S8, the first PCs are not the most informative, whereas subsequent PCs exhibit a broad distribution of relevant information. This supports the use of proper machine learning tools to make the best use of this distributed information.

**FIGURE 3**

**Signature network of links supporting the classification**

An important advantage of the MLR over kNN is its efficiency in characterizing the links that contribute to the classification. We used recursive feature elimination (RFE, see Methods for details) to rank the links according to their weight in the classification and chose the lowest number of links that achieved the maximum classification performance. In comparison, the same procedure with kNN would require an incommensurate amount of computational power, recalculating the closest neighbor for all combinations of links (here the number of links is p >> 1000; see Methods for further discussion). The resulting support network for dataset A1 had 18 links, to be compared with 44 links for dataset B. In both cases, subject identification using only those links achieved perfect accuracy (90% of all available sessions were used for training and 10% for testing, see Figure S9). The two support networks are shown in the same matrix (Figure 3D): remarkably, the networks are very sparse and non-uniformly distributed across the whole brain. This is the signature of the most subject-discriminative ROIs: frontal and cingulate cortices, as well as the temporal and occipital regions, seem to play a major role here. It is worth noting that the adjacency matrix is not symmetric, which implies different roles for nodes as receivers (especially frontal ROIs) or senders (cingulate).

The sparsity of the signature in Figure 3D hides the fact that the rankings for dataset A1 and B are to some extent aligned (PCC=0.59, p-value<<10-50), indicating that similar neural networks characterize individuals in two disjoint sets of subjects. To further measure the overlap between these networks, we selected for each dataset the subset of links with the highest ranking and computed the number of common links. Figure 3E shows that the proportion of common links exceeds by far its expectation under the hypothesis of random rankings (shaded gray area). This indicates a good agreement between the support networks from the two datasets even at the single-link level.

**Twofold classification of subject identity and behavioral condition**

Finally, we used Dataset C to extract a signature for the subject identity and another for the behavioral condition. This is schematically depicted in Figure 4A, with three fictive dimensions: the information about subject identity corresponds to the x-axis and information about the condition to the z-axis; the session-to-session variability, that has to be ignored, spreads along the y-axis. In this idealized 3D scenario, it is possible to classify a session with respect to both subjects and conditions using different dimensions of the data. In the high dimensional case, this occurs when different sets of links support the two classifications.

Using MLR and EC, we achieved very high performance (accuracy > 90%) for subject identification and perfect classification for the condition.

We then sought the smallest subsets of links that achieve the maximum performance of each classification, as detailed above (see Figure 4B and Methods for details). Both support networks were again very sparse and distributed across the brain, as can be seen in their adjacency matrix (Figure 4C). More links are necessary to identify the subjects (57) than the behavioral conditions (13), indicating a higher complexity for the former.

As before, we used RFE to rank the links according to their contribution to the classification. We computed the number of common links for the subject and condition identifications, which fell within the expected values with the null hypothesis (Figure 4D). This indicated that distinct subsets of links are relevant for the subjects' identity and behavioral condition.

**FIGURE 4**

Similar to Datasets A1 and B, subject identification of Dataset C largely concerns the frontal and cingulate systems. Condition identification is also supported by occipital and temporal cortices, which are expected to have the strongest activity modulations during movie viewing. The top panels in Figures 5A and B represent the two support networks such that the directed nature of links can be appreciated. Apart from two small components, the subject network is almost fully connected with several central nodes (hubs, indicated by their large size) located in frontal and cingulate regions. On the contrary, the network for condition is segregated with small isolated components. The bottom plots (Figure 5) show the lateralization of the support links, stressing the asymmetries between the two hemispheres: most of the important links are ipsilateral (i.e. within the same hemisphere) and many belong to the left hemisphere for the subject network, whereas they are mainly contralateral for the condition network.

**FIGURE 5**

**DISCUSSION:**

In this study, we have proposed a framework to predict the identity of subjects as well as their condition from fMRI time series, by robustly extracting discriminative signatures about subject/condition differences. We obtain very sparse signatures, supposedly because of the datasets used (30 subjects maximum; 2 conditions). Their size is expected to increase with the complexity of the “environment” to represent (many subjects, many tasks); resources are becoming available to test this quantitatively [49 ,25]. Importantly, we have proven that such EC-based signatures are robust to the session-to-session variability, and can be obtained relying on a limited number of sessions (4-5 recordings of 5 minutes each). Proper machine-learning tools such as MLR are necessary to efficiently extract those signatures. We now discuss specific points.

The fundamental advancement of our study is the development of a reliable and well-benchmarked method, extending the previously published proofs of concept [35,15]. EC discriminates subjects better than corrFC irrespective of the number of sessions per subject used, and for both classifiers MLR and kNN (Figures 2 and 3). In particular, the generalization capability for EC is much more robust than FC when the classification becomes harder (few sessions per subject or many subjects to identify, see Figure 3B). This confirms that the BOLD temporal structure – captured by the EC – reflects the identity of the subject [35], as previously shown for a task involving (or not) attention [28] or for wake versus sleep [36]. Here the focus was on EC because it performed better than Σ estimates in subject identification, but it has been recently shown that Σ is strongly affected when engaging a task condition [22], so Σ might further improve the classification for conditions, in particular involving sensory stimuli.

Our whole-brain dynamic model is a continuous-time network with linear feedback that incorporates topological constraints from SC. EC corresponds to a maximum-likelihood estimate and can be very efficiently calculated for the whole brain with ~100 ROIs and each session with ~300 time points per ROI [21,22]. Our results show that, although the dynamic model and estimation procedure are a simplification compared to the dynamic causal model with hemodynamics and Bayesian machinery [44,20], it nonetheless provides powerful signatures that can be used for discrimination between subjects and conditions. Our study has focused on two coarse parcellations covering the whole brain [46] or cortex [27]. Although the two parcellations where applied to different datasets we did not observe significant difference in the performance of the classifiers. Much work has been done recently to correct the bias due to the use of specific parcellations [8]; for our purpose, more refined parcellations may entail better discriminability in higher-dimensional spaces, but raise issues for the EC estimation robustness. On another ground, preprocessing using PCA was not found to significantly enhance the performance here. Nonetheless, PCA may be useful for datasets with larger number of subjects and conditions. In the end, the generalization capability is *the* criterion for the classification performance and further work is needed to define a suitable level of detail for applications with many subjects and conditions.

We have found that very few links (<4%) were sufficient to classify perfectly 30 subjects from Dataset B (Figure 3C) and both subjects and conditions in Dataset C (Figure 4D). For a larger cohort [15] and more tasks [25], we expect this number to grow and the infra/supra-linear dependency with the subject number should be addressed carefully. Those support networks for the twofold classification (subject and condition) show several noticeable differences (Figure 5). The subject network is large, almost fully connected, distributed over the two hemispheres (with more links within the left one) and concentrated in the cingulate and frontal areas. This suggests subject-specific dynamics within areas involved in high-level functions and overlapping with the default mode network [39]. This interpretation of EC in terms of brain communication comes from the directed nature of EC, which considers the propagation of BOLD activity. It follows that the discriminative EC patterns may reflect heterogeneities in the interactions between the different neural subsystems (e.g., frontal to cingulate in Figure 5) and the propagation of information between them [12,13]. We also found a much higher percentage of contralateral links for condition than subject. This is in line with strong inter-hemispheric interactions observed for the same dataset with community analysis [22]. As expected with the movie viewing condition studied here, links in the visual and temporal areas are discriminative.

The idea of personalized medicine to characterize brain disorders at the patient level is emerging [49], using neuroimaging techniques [34] as molecular and genetic approaches before. The development of tailored therapeutic protocols [42] that aim to optimize recovery and minimize adverse effects requires quantitative tools that allow for a precise diagnostic of the patient's evolution. The general scheme we have in mind for diagnostic is thus to follow a patient's trace over time in the (high-dimensional) EC space: as schematized in Figure 4A, the classification for condition would correspond to healthy opposed to various pathologies, from which one (or several) signature(s) have been extracted from resting-state [26] or task-evoked fMRI. The generalization capability of prediction methods to future (unseen) data [30] is crucial in such clinical conditions. To this end, our method disentangles fMRI signatures related to the subject and condition, while properly conditioning out the day-to-day variability (as uninformative intrinsic noise). This provides a practical solution to the recent criticism that “a major reason for disappointing progress of psychiatric diagnostics and nosology is the lack of tests which enable mechanistic inference on disease processes within individual patients” [45]. Importantly, the goal is not so much to discriminate between subjects as to prevent individual signatures from mixing with those for pathologies. We expect the latter to be much more complex [5] than the very sparse signature for movie viewing (Figure 4-5). The framework could be extended to the three-fold space (subject, pathology, task) as specific tasks may reveal powerful signatures for certain pathologies, such as memory exercises for Alzheimer [31].

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