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Brain Fingerprinting

A signal processing perspective

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The 17th-century physician Marcello Malpighi observed the existence of distinctive patterns of ridges and sweat glands on fingertips, catalyzing its widespread use in forensics, but also, more generally, inspiring research to develop ways to identify individuals based on unique biological characteristics. Today, this concept has expanded vastly into diverse data, and the term *biometrics* has been introduced to encompass all methods of automated human recognition, such as fingerprint, face, iris, retina, and voice analysis [1]. More recently, neuroimaging data have been explored for this purpose, giving rise to the concept of "brain fingerprints," derived from patterns of functional networks. This perspective challenges the classical view of neuroimaging analysis, which treats individuals as repeated measures of a population-level effect, where interindividual differences are considered noise rather than signal. In contrast, intersubject variability here represents the key feature in the data allowing the unique representation and identification of an individual. This marks a paradigm shift that has sparked a wave of new interdisciplinary research, branching from neuroscience to machine learning and signal processing.

Introduction

At the intersection of neuroimaging and network science, the field of brain connectomics has emerged as the study of how brain regions interact with one another, and how such connectivity patterns support mental processes and behavior in health and disorder [2], [3]. In their seminal work, Finn et al. [4] introduced the concept of "brain fingerprints" (or "connectome fingerprints"), which are based on the functional connectome (FC) derived from functional magnetic resonance imaging (fMRI) data. They showed that individuals can be reliably identified among more than 100 participants by matching FCs across sessions, achieving identification rates above 90% for resting state and between 54% and 87% for task conditions. This seminal work demonstrated that functional connectivity profiles are both unique and consistent—resembling a fingerprint—and can be recovered with high accuracy. Subsequent studies in healthy adults [5], [6], [7] replicated these findings,

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further showing that FC-based fingerprints remain stable over years [8].

Brain fingerprinting can be regarded as an extreme form of phenotyping: Rather than linking neuroimaging features to traits, such as personality or age, it leverages the uniqueness of each individual's connectivity profile. The observation of these unique brain patterns has underscored the limitations of group-level statistics—long considered the standard in FC research—by showing that averaging across participants can obscure individual-specific signatures. While group studies remain valuable for population-level insights, focusing on individual fingerprints may better characterize specific brain functions and inform clinical applications. In particular, the investigation of brain fingerprints holds promise for clarifying the currently unclear distinction between idiosyncratic and degenerative brain patterns characterizing different conditions. Focusing on person-specific brain connections could improve diagnostic precision and guide the development of personalized therapeutic strategies and targeted interventions. Yet, many open questions remain concerning the nature and properties of intersubject variability in the way the brain reacts and functions. For example: What exactly are the components that make fingerprinting possible, such as temporal and signal variability, modality, motion, task-rest differences, or anesthesia- and drug-induced states? What is the relationship between fingerprints and behavior? And finally, can we use brain fingerprints to better investigate individual profiles of brain connectivity across disease? Current research is addressing these questions, with the ultimate goal of harnessing brain fingerprints to investigate brain function and evolution in both health and disease.

In this article, we outline the conceptual foundations of brain fingerprinting, which leverage the unique functional imaging features of each individual's brain. To avoid confusion, we emphasize that this is distinct from the field of magnetic resonance fingerprinting [9], an acquisition scheme aimed at optimizing the uniqueness of magnetic resonance signals originating from different tissues. In the following, we present the core principles of brain fingerprinting together with its extensions, adopting a perspective rooted in signal processing and machine learning to reformulate its basic concepts. This enables us to identify synergies between disciplines and to highlight the most promising avenues for ongoing and future research.

Brain fingerprinting methodology

The first step for brain fingerprinting is to extract FCs from the acquired and preprocessed fMRI runs (see "From Functional Magnetic Resonance Imaging Time Series to the Functional Connectome" for a detailed description). Conventional preprocessing includes brain volume realignment, spatial smoothing, regression of nuisance signals (such as motion parameters, average white matter and cerebrospinal fluid signals, and scanner drifts) as well as brain parcellation. These choices, along with acquisition protocols, can influence FC metrics and, consequently, fingerprinting [10]. Notably, a normalization to a standard space may obscure individual differences and is unnecessary here, as FC matrices—not brain volumes—are the objects compared across subjects. The obtained FC for a subject $i = 1,\ldots,N_S$, and run $r = 1,\ldots,N_R$, is an $N \times N$ connectivity matrix $\mathbf{C}_i^{(r)}$, where N indicates the number of brain regions. The initial concept of brain fingerprinting focused on identifiability of an individual based on the FC [4], [11], which was matched to the subject with the closest FC of another scanning session. The inputs are, therefore, the FCs of all subjects collected from two runs $N_R = 2$ (day 1 and day 2). Then, the upper-triangular part of the FCs is unfolded into a vector $\mathbf{c}_i^{(r)}$ of length $M = N(N-1)/2$ that can be compared with other subjects and runs using a similarity metric, such as inner product or Pearson correlation. An overview of the brain fingerprinting procedure in its basic form [4] is illustrated in Figure 1. We can remark that this canonical approach, most often applied in literature, remains naïve to the topology of the network, ignored in the matrix unfolding step.

Following the original work of [4], the vast majority of the studies of the last decade use Pearson's correlation as a similarity metric between test/retest connectomes [5], [8], [12], [13], [14], [15], [16], [17]. More rarely, a distance metric is employed, such as Euclidean distance [18] or cosine distance [19]. The use of geometry-aware metrics defined in non-Euclidean space, such as geodesic distance, has also been preliminarily attempted [20], [21], and implications of these advances on fingerprinting performance will be detailed in the "Topological Data Analysis and Geodesic Distance" section.

In subsequent work, the so-called *identifiability matrix* was defined by the similarities of FCs between all pairs of subjects scanned at two sessions [5]. The comparisons of all pairs of subjects i and j can be stored into the $N_S \times N_S$ matrix:

$$\mathbf{I}[i,j] = \mathrm{sim}(\mathbf{c}_i^{(1)}, \mathbf{c}_j^{(2)}). \tag{1}$$

The predicted subject for the second run of subject j is then

$$\mathrm{predict}(j) = \underset{i=1,\ldots,N_S}{\mathrm{argmax}}\, \mathbf{I}[i,j] \tag{2}$$

which will render an answer based on which FC of the first run is closest to $\mathbf{c}_j^{(2)}$. Consequently, the accuracy can be computed as the percentage of correct matches across all subjects.

The structure of this matrix can be further analyzed by the difference between diagonal and off-diagonal elements, introducing the idea of "differential identifiability"; i.e., the amount of separation between individuals becomes a performance metric instead of the bare success rate of identification. In particular, the diagonal elements $\mathbf{I}[i, i]$ represent self-similarity scores between the two runs, and the off-diagonal elements $\mathbf{I}[i, j]$, for $i \neq j$, represent cross-subject similarities. The difference between diagonal and off-diagonal elements quantifies differential identifiability:

$$I_\Delta = \frac{1}{N_S}\sum_{i=1}^{N_S}\left(\mathbf{I}[i,i] - \frac{1}{N_S - 1}\sum_{j\neq i}\mathbf{I}[i,j]\right). \tag{3}$$

This performance metric provides a useful alternative to mere identification accuracy. Indeed, higher I_Δ indicates better

distinctiveness of individuals [5]. The original formulation of differential identifiability has been extended by using individualized z-scored version of (3) [22], or using the standardized version of I_Δ (Cohen's d) to better interpret intersubject differences. Differential identifiability tends to decrease as the number of subjects increases, since larger cohorts raise the likelihood of similar FC profiles and make individual fingerprinting more challenging, yet more realistic [23]. Adequate sample sizes are therefore recommended to obtain robust estimates of fingerprinting performance.

Denoising of brain fingerprints

Since brain fingerprints are based on FCs, their specific graph nature can be exploited to come up with metrics in the feature space, such as graph embedding [19]. This can help "denoising" brain fingerprints by selecting the most relevant information for subject identification. Sources of noise for fingerprints can be varied; e.g., the nature of the signal itself [blood oxygenation level dependent (BOLD) signal dependent on vascular processes, electroencephalography (EEG)/magnetoencephalography (MEG) signal confounded by crosstalk effects], acquisition, and processing choices, like temporal resolution [24].

Dimensionality reduction techniques, such as principal component analysis (PCA) or singular value decomposition (SVD), have been applied to improve the identifiability of brain fingerprints by maximizing variance in the data. In fact, both techniques can be employed to condense high-dimensional connectome data into low-dimensional decompositions, which showed indeed to maximize differential identifiability [5]. Let $\mathbf{X} = [\mathbf{c}_1^{(1)} \ldots \mathbf{c}_{N_S}^{(N_R)}]$ be the matrix with all unfolded FCs, over subjects and sessions. Therefore, $\mathbf{X}$ is an $M \times (N_R N_S)$ rectangular matrix. SVD then factorizes this matrix as

$$\mathbf{X} = \mathbf{U}\mathbf{S}\mathbf{V}^T \tag{4}$$

From Functional Time Series to the Functional Connectome

Functional time series are acquired from advanced techniques, such as functional magnetic resonance imaging (fMRI), electroencephalography (EEG), or magnetoencephalography (MEG) during resting-state; i.e., while the subject is instructed to stay still, without performing any task. While EEG and MEG record brain electrical signals and magnetic fields at different brain surface locations, fMRI signals are blood oxygenation level dependent (BOLD), and represent a proxy of brain activation thanks to neurovascular coupling mechanisms. Careful preprocessing specific to the technique used must be performed, to remove nuisance components (i.e., motion, confounding signals from neighboring tissues, recording-related artifacts). In addition, filtering in different frequency bands and source localization are often performed in the case of EEG/MEG, the latter to identify the anatomical sources of recorded scalp measures. These choices are key to the following steps (Figure S1), and must be carefully evaluated. Brain activity signals at each considered brain location (voxel) are averaged in a set of N brain regions, given by a template parcellation (atlas). This can be based on function, anatomy, or multimodal information and typically encompasses few hundred regions. Robustness of results with respect to the atlas choice is important to assess. Pairwise correlations between the N regional time courses are then computed (in the simplest case using Pearson's correlation), and yield the so-called *functional connectome* (*FC*); i.e., a symmetric $N \times N$ matrix containing pairwise correlation values. According to this definition, FC does not relate to any particular direction or structure of the brain, but rather highlights correlated activation that can emerge from mono- and polisynaptic structural connectivity.

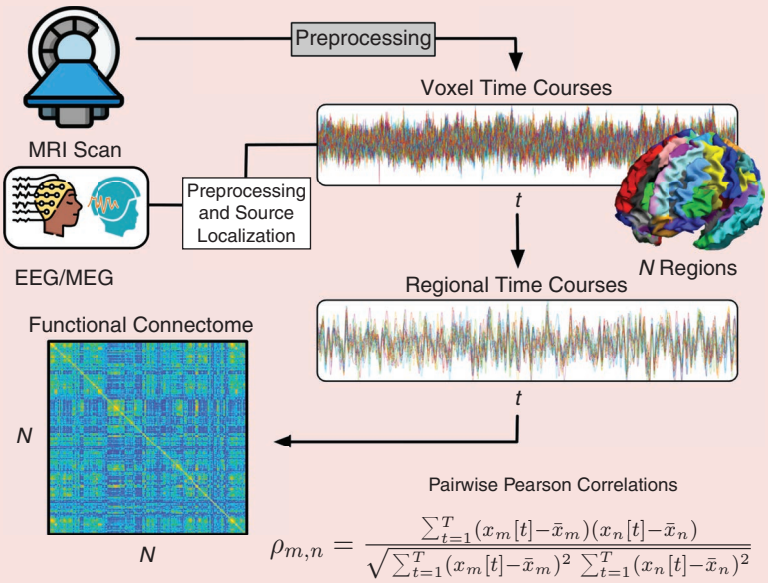

FIGURE S1. From the acquisition to the functional connectome (FC): main steps to obtain FCs from functional brain data.

where the columns of $\mathbf{U}$ are the singular vectors representing FC profiles, and those of $\mathbf{V}$ are their association to subjects and runs. The diagonal of $\mathbf{S}$ contains the singular values that can be squared to relate to the explained variance of the components. Those with large variance capture the most stable and subject-specific connectivity patterns, whereas low-variance components capture variability not directly related to subject identification [5], [19]. By retaining the top K components, a denoised version of the FCs can be reconstructed for each subject i and run r:

$$\mathbf{X}_K = \sum_{k=1}^{K} s_k \mathbf{u}_k \mathbf{v}_k^T. \tag{5}$$

The choice of K can be determined either through data-driven approaches, such as maximizing differential identifiability, or by systematic rules, like retaining a certain percentage of explained variance; however, data-driven methods are often preferred for optimizing fingerprinting performance [5], [25].

Different studies have demonstrated the effectiveness of SVD in improving subject-identification rates [19]. In these studies, SVD was applied to extract latent fingerprints by identifying and removing noisy (i.e., associated with physiological or scanner effects) components through optimization of the differential identifiability score:

$$I_{\Delta,K} = \frac{1}{N_S} \sum_{i=1}^{N_S} \left(\mathbf{I}_K[i,i] - \frac{1}{N_S - 1} \sum_{j \neq i} \mathbf{I}_K[i,j] \right) \tag{6}$$

where $\mathbf{I}_K$ represents the identifiability matrix computed using the FCs by retaining K components.

While this denoising step enhances the reliability of individual fingerprints by removing noninformative or task-induced variability [5], it should be noted that it is not compatible with the machine learning viewpoint of prediction of unseen data; i.e., even if the SVD is unsupervised with respect to the subjects' identities, it has "peeked" into all data, including the run that is to be identified. Instead, the data can be split into training and test runs, SVD only applied to the FCs of the training runs, and then project the FC of the test run onto these first K components as $\mathbf{c}_K = \Sigma_{k=1}^{K} (\mathbf{u}_k^T \mathbf{c}) \mathbf{u}_k$.

As a specific application of SVD, PCA identifies the directions of maximum variance in the data, which has strong implications for identifiability maximization [5], especially across fMRI sessions acquired in different scanners [26] (multisite fingerprinting), and with different acquisition parameters [24] (repetition time denoising). In fact, scanner-related variability systematically diminishes the identifiability of FC fingerprints, although longer scan durations were shown as useful to minimize this effect [27]. Harmonization techniques can also be incorporated into FC studies, potentially preventing spurious findings and improving the reliability of results [28]. Our recommendation would be to use PCA denoising in such scenarios where individual identifiability might be corrupted by systematic noise sources.

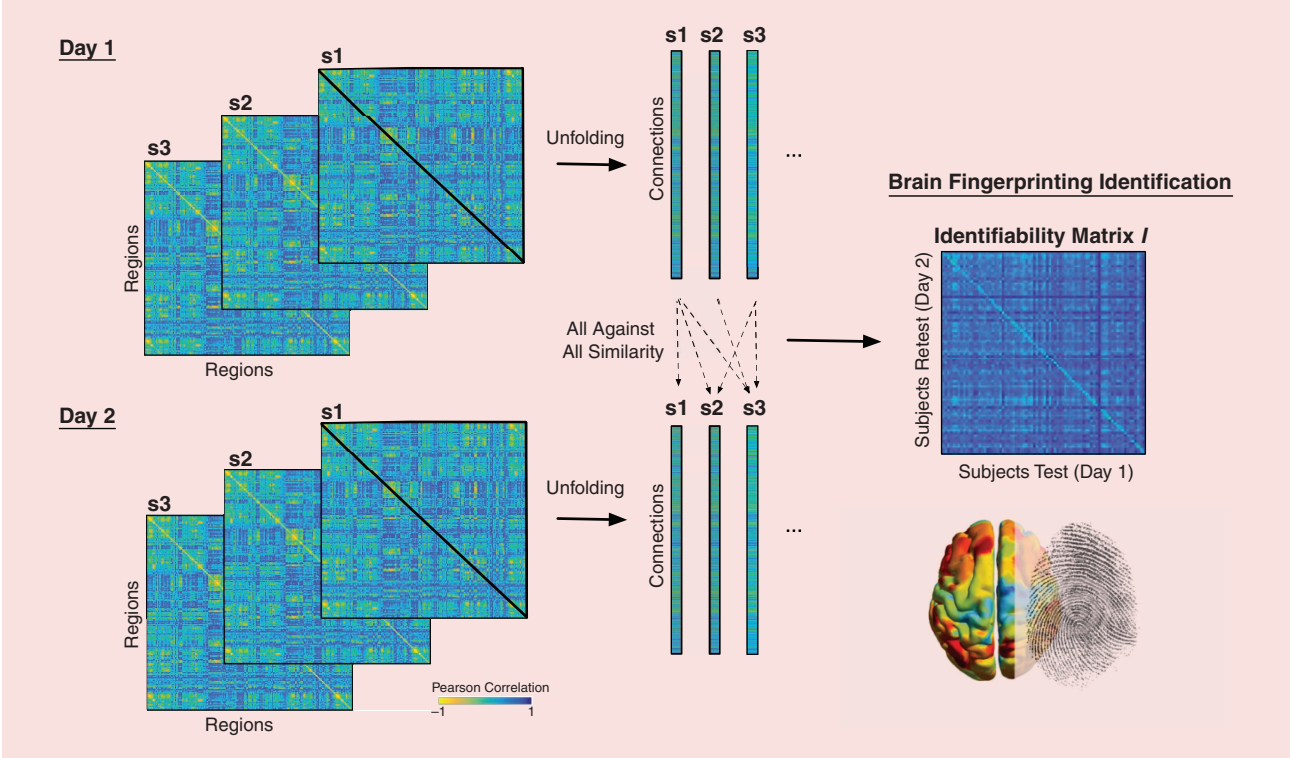

FIGURE 1. Brain fingerprinting methodology. Subjects undergo two fMRI acquisitions (day 1 and day 2), from which FCs are obtained. The upper triangular part of the symmetric FC is first unfolded and then compared with all subjects, across the two sessions. Similarity values are stored in the so-called *identifiability matrix* $\mathbf{I}$.

Intraclass correlation and reliability of fingerprints

A key aspect for the interpretability of fingerprints in the neuroscientific field is the investigation of brain regions or connections that contribute most to the brain fingerprint. Intraclass correlation (ICC) has been widely used to assess the reliability and stability of a functional connection within and across individuals. In particular, for a connection between regions m and n we obtain [5]

$$\mathrm{ICC}[m,n] = \frac{\sigma_b^2[m,n] - \sigma_w^2[m,n]}{\sigma_b^2[m,n] + (N_R - 1)\sigma_w^2[m,n]} \tag{7}$$

where σ_b^2 is the between-subject mean-square variance, σ_w^2 is the within-subject variance, and N_R is the number of repeated measures (e.g., scanning sessions). Regions or connections with higher ICC values contribute more to identifiability. Several studies have shown that connections between brain regions of higher-order cognitive networks, such as the default mode network and frontoparietal network, exhibit higher ICC values compared to connections of unimodal regions, such as sensory-motor ones during resting-state [5], [29], [30], [31]. This, however, was shown to depend as well on the temporal scale of the investigation, with lower-order regions peaking at shorter time-scales, and higher-order regions increasing their ICC when longer windows (or the whole acquisition time) are considered [32]. Specific cognitive states driven by a task would also influence regional ICCs, with a shift in the peak toward regions engaged by the task [27]. Moreover, ICC can be used to optimize preprocessing choices by identifying the most stable functional connections that contribute to brain fingerprinting [31]. The ICC-based selection of features has been shown to enhance the robustness of identification models and improve cross-run reproducibility of fingerprints [5]. The workflow for feature selection established in previous work proceeds in three steps:

1) *Distribution-based thresholding:* Apply percentile cutoffs on the ICC distribution to retain the most reliable edges.
2) *Cross-validated optimization:* Evaluate different cutoffs in cross-validation to identify the threshold that maximizes out-of-sample identifiability and prediction [14], [30].
3) *Robustness checks:* Use bootstrapping and permutation testing to ensure results are stable and not driven by sampling variability [15].

Brain fingerprinting revisited

The concept of brain fingerprinting has been extended and generalized in different ways. In particular, revisiting brain fingerprinting from the network topology, machine learning, and signal processing perspectives allows us to pinpoint some future promising extensions of this framework.

Topological data analysis and geodesic distance

One important aspect of conventional brain fingerprinting is the fact of considering the feature vectors as lexicographically unfolding of the FCs (see "From Functional Magnetic Resonance Imaging Time Series to the Functional Connectome"), and thus ignoring the nature of the latter. Vectorized FC features are then compared by using similarity metrics, such as Pearson's correlation or, more rarely, Euclidean distance, implicitly assumed to lie on a linear high-dimensional space. Instead, FC lies inside or on top of a high-dimensional nonlinear manifold (brain surface), and considering this fact might improve FC investigation and fingerprinting accuracy [20]. The use of non-Euclidean geometry, in particular of Riemannian geometry, allows us to define FC as lying on a curved surface with positive curvature (e.g., a sphere), therefore yielding a more realistic representation. In this context, the geodesic distance in the space of positive semidefinite matrices provides an interesting alternative to define a distance metric between two FCs $\mathbf{C}_i$ and $\mathbf{C}_j$:

$$\mathrm{dist}(\mathbf{C}_i, \mathbf{C}_j) = \|\log(\mathbf{C}_i^{-1/2}\mathbf{C}_j\mathbf{C}_i^{-1/2})\|_F \tag{8}$$

where $\log(\cdot)$ denotes the matrix logarithm, and $\|\cdot\|_F$ is the Frobenius norm. This distance metric accounts for the non-Euclidean structure of correlation matrices, therefore, for the nonlinear curved surface that FC lies on [20], [21], and [33]. In particular, using geodesic distances as dissimilarity metrics helps in yielding higher subject identifiability in task conditions [20]. At the same time, geodesic distance is more sensitive to deviations from manifold assumptions than simpler metrics, especially under noise, or sparse sampling. Careful preprocessing and regularization are necessary to ensure reliable fingerprinting performance in noisy or low-rank functional connectivity data. However, to incorporate the geometry but keeping the advantages of the Euclidean space (e.g., independent features, and consequent generalizability and stability of machine learning algorithms), a tangent Euclidean space can be created upon the manifold, and (regularized) FC matrices can be projected on it, yielding tangent FCs; i.e., matrices of the same dimensionality as original FCs, but defined on a Euclidean space and therefore analyzable with Euclidean methods [Figure 2(a)]. Tangent FCs, whose elements can be considered as independent features, were shown to represent better biomarkers of age and brain conditions, as well as to own higher fingerprinting power [33].

Furthermore, optimal regularization of FCs ensures invertibility, improving geometry-aware fingerprinting. Let $\mathbf{C}_i$ be a rank-deficient FC, then regularization is performed by adding the diagonal as

$$\mathbf{C}_i \rightarrow \mathbf{C}_i + \tau\mathbf{E} \tag{9}$$

where τ is a small positive regularization parameter and $\mathbf{E}$ is the identity matrix. The optimal amount of regularization for input FC matrices was also investigated, showing that fine-tuning this parameter specifically for each dataset leads to systematically higher fingerprints [21]. In the same article, the authors also discuss the potential influence of acquisition and other preprocessing choices on the regularization parameter. For this reason, defining τ based on an existing rule is not recommended; instead, an adaptive selection that optimizes fingerprinting performance appears more effective.

Machine learning

Today's perspective of brain fingerprinting moves the investigation of connectivity beyond group-level inference, shifting instead toward leveraging intersubject variability as a source of signal rather than noise for connectivity decoding. This naturally resonates with the machine learning viewpoint, where fingerprints acquired from different subjects in one session can be seen as feature vectors of a training sample, used to predict an unknown feature vector from a separate (retest) session. The identifiability matrix can likewise be considered as the classical distance/similarity matrix among the individuals to be identified. When embedding fingerprinting within a machine learning framework, it becomes particularly important to carefully separate training and test datasets, avoiding dimensionality reduction techniques that require prior aggregation of the full dataset (see the "Denoising of Brain Fingerprints" section). Only a few studies have explicitly adopted this approach by proposing subject classification architectures, and much remains to be explored. For example, future work could move beyond the simple nearest-neighbor classification, which is still the most common method. The identifiability matrix can also be refined within a cross-validation framework, an aspect not always implemented in current studies. Along these lines, Hannum et al. recently explored the accuracy and reliability of five different machine learning techniques [linear discriminant analysis (LDA), support vector machine (SVM), multilayer perceptron neural network, nearest-centroid, and correlation-based classifiers], showing a near-perfect ability of some of these to perform subject fingerprinting [34]. In particular, LDA outperformed the other approaches with an accuracy of 99%. In fact, empirical evidence suggests that individual fingerprints are largely linearly separable in feature space (e.g., vectorized FC matrices), which may explain the superior performance of LDA compared to nonlinear classifiers in this context. In addition, because it relies on fewer parameters, LDA is less prone to overfitting in high-dimensional, small-sample settings, such as fingerprinting studies. However, dimensionality problems occur when dealing with finer parcellations, yielding tens of thousands of connections. In [35], researchers addressed this issue by adopting a leave-one-out cross-validation setting with a SVM classifier to perform fingerprinting, reaching similar performances.

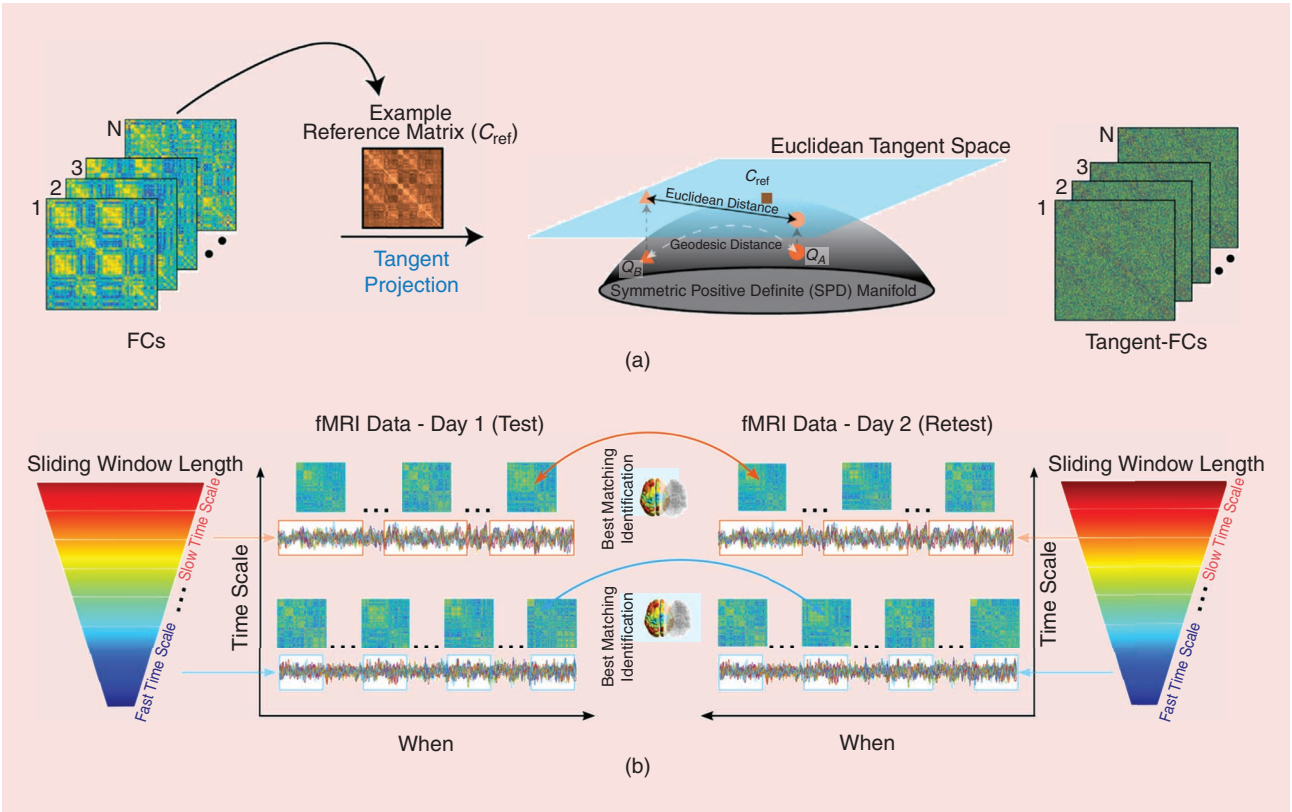

FIGURE 2. Extensions of the canonical fingerprinting framework. (a) As conventional fingerprinting is based on the unfolding of FC matrices, it completely disregards the underlying geometry of the brain. An alternative defines the FC metrics as lying on a manifold with positive curvature, representing the brain surface. The geodesic distance can be used as a distance metric to compare FCs in the space of symmetric positive definite manifolds. However, the Euclidean distance between the projection of FCs in a Euclidean tangent space can also be used for simplicity. $\mathbf{C}_i$ is a regularized input FC matrix, projected on a reference matrix $\mathbf{C}_{\text{ref}}$ in a tangent Euclidean space (adapted from [33]). (b) As originally defined, fingerprinting does not account for temporal variations of FCs. Considering the time-varying aspects of FCs, computing it in temporal windows of different lengths instead of on the whole acquisition time allows for investigating the optimal timescale at which brain fingerprints integrate information. Longer temporal scales show higher fingerprinting power, even if "bursts" of identifiability are present at shorter scales as well (adapted from [32]).

Looking ahead, targeted extensions that leverage neural network architectures for fingerprinting [36] are conceivable, although a persistent challenge is the limited sample sizes typically available in neuroscience research. Incorporating self-supervised learning could help refine individual differentiation. First applications of recurrent neural networks [37] in brain fingerprinting have shown promise in capturing dynamic brain features more effectively. In [38], a conditional variational autoencoder network was combined with a sparse dictionary learning module, and fMRI state information was embedded in the encoding and decoding processes to enhance the intersubject variability for better fingerprinting. From a multimodal perspective, graph neural network architectures that integrate fMRI and EEG data could further enhance the detection of common individual features across neuroimaging modalities.

Integrating different imaging/signal recording modalities for fingerprinting appears to be a promising future avenue to leverage the complementary information of different approaches.

Alternatives to FC-based fingerprints

FCs derived from resting-state and task fMRI have been widely used, but they are not the only type of brain fingerprint obtainable from neuroimaging data.

First, alternative estimators of FC could be considered. For example, effective connectivity aims at modeling directed paths of FC that are posited from known structural connectivity, revealing causal interactions. A preliminary work recently introduced the concept of "causal fingerprinting," showing undergoing efforts to leverage causal dynamics for brain fingerprinting [39]. Along these lines, precision-matrix estimators, essentially the (regularized) inverse of the FC matrix, offer a multivariate alternative to the conventional FC features with closer correspondence to underlying structural connectivity [40]. Future research is needed to determine whether such alternative connectivity estimators could improve fingerprinting performance or deepen its interpretability.

Second, other modalities than fMRI can be used to extract brain features. MEG and EEG are other functional imaging techniques providing subject-specific features that showed successful fingerprinting performance at rest [14], [15], [18], [22], [41], [42], as well as in task [16], [43]. Even if fMRI-based connectomes generally yield higher identification rates due to the rich spatial resolution and stable temporal dynamics over minutes-long recordings, studies on MEG fingerprints showed stronger association with behavioral and clinical features [14], [15], [44]. This might be due to intrinsic differences in the nature of the signals, with large-scale electrophysiological connectivity patterns potentially carrying greater behavioral and clinical relevance than hemodynamic measures, but also differences in their respective temporal scales. Indeed, access to rapid timescales allows MEG-derived FCs to be obtained for different frequency bands, which may better reflect behavioral and clinical traits. These, in turn, show varying fingerprinting performance [15], [22], indicating that they contain specific, selective information. In particular, higher accuracy was reached when using FC features from the alpha [15] and beta ranges [15], [22], with respect to other frequencies. These signals are believed to play an active role in information processing, attention and top-down control mechanisms, possibly reflecting internal cognitive models that are inherently more specific of each individual [22]. Methods of multivariate time series classification have also been successfully applied to M/EEG time courses to directly classify subjects from short temporal segments [42], [43]. Similarly, simple spectral features of the signal (e.g., power spectral density or the power spectrum aperiodic component) have proven to be valid alternative to FCs, with equally successful individual differentiation [18], [22].

Third, anatomical features of axonal bundles in white matter, extracted from diffusion-weighted MRI (dMRI), were also shown to yield satisfactory fingerprinting performance [13], [45], demonstrating higher intersubject versus within-subject variability, when comparing two separate acquisition sessions. The increased stability of structural connectomes over time (lower intraindividual variability across sessions compared to FC) enhances subject identification, which is further improved when high spatial resolution (vertex-wise) structural connectomes are used [13]. In addition, structural connectivity stability characterizes humans from early life stages, in contrast to a faster dynamically evolving FC observed in children, reflecting their constant acquisition of new skills and adaptation to the environment [46], [47].

Finally, as discussed in the next section, recent work has highlighted how multimodal approaches may enhance fingerprint robustness by integrating structural and functional characteristics, instead of considering them separately [12], [35].

Multimodal fingerprinting and graph signal processing

Integrating different imaging/signal recording modalities for fingerprinting appears to be a promising future avenue to leverage the complementary information of different approaches [48]. For example, combining EEG and MRI biometrics would help compensate for the weaknesses of the two technologies, namely the low temporal resolution and delayed response of the BOLD signal, and the low spatial resolution and source localization issue in EEG. Structural information could also be integrated with functional information for fingerprinting purposes. In fact, while the accuracy of FCs for identifiability is well known, structural connectomes (from dMRI) were shown to increase stability throughout neurodevelopmental stages from early to adult age [46]. Considering both sources of information might reveal deeper insights into which mechanisms of the brain are key features of brain fingerprinting. Combining structural, functional, and dMRI at high spatial resolution (voxel-level), Mansour et al. found that multimodal cortical gradients of individual uniqueness reside in the association cortices [13]. Interestingly, the authors also compare the different imaging modalities, finding that while morphological

brain properties encode more information about the individual, FC better predicts behavioral features.

From a signal processing perspective, the recent emergence of graph signal processing (GSP) offers valuable tools for multimodal brain fingerprinting. In particular, the concept of fingerprints that combine structural and FCs could benefit from the GSP framework, where signals (e.g., functional) are defined on a graph domain (e.g., structural graph). Recent work explored this approach by replacing the connectome-derived fingerprint with a map of structure–function dependencies quantified via GSP-based spectral filtering, demonstrating that this representation also carries subject-specific information [35]. Notably, both nodal and edgewise metrics of structure–function coupling were found to outperform corresponding FC features in subject identification, suggesting that the portion of functional signal, which is more decoupled from structure, carries the most of the fingerprinting power.

Another effort in this direction has been made in [12], where a new framework based on manifold approximation was proposed to generate brain fingerprints from multimodal imaging data. Specifically, a subject proximity graph was constructed using multimodal imaging features (from T1/T2-weighted MRI, dMRI, and resting-state fMRI), and projected into a low-dimensional manifold via spectral embedding. Fingerprinting of new unseen subjects was then performed, using compact multimodal features, which demonstrated increased discriminative power with respect to unimodal ones, as well as increased similarity between monozygotic twins relative to dizygotic twins or unrelated individuals.

Temporality of brain fingerprints

The robustness of brain fingerprints has motivated investigations into denoising strategies and temporal dynamics. A key aspect of brain fingerprinting is its resistance to noise and signal variation due to temporal resolution [24], as well as its resilience to data acquisition heterogeneity [49]. Studies have shown that some functional connections contribute more strongly to identifiability than others, with higher-order cognitive networks (e.g., frontoparietal and default-mode networks) showing greater stability and specificity compared to sensory-motor regions [5], [32]. Importantly, the temporal stability of brain fingerprints varies across timescales, with short-term fluctuations influencing identification accuracy. Recent work suggests that while long-duration scans provide stronger and more reliable fingerprints, individual identifiability can still be preserved in shorter recordings due to transient bursts of high identifiability [32] [Figure 2(b)]. These findings highlight that different timescales capture complementary aspects of brain fingerprints, where rapid fluctuations may reflect state-dependent changes, while long-term averages encode stable, trait-like characteristics of an individual's connectome. This interplay between signal duration and identifiability emphasizes the importance of choosing optimal temporal windows for brain fingerprinting applications, particularly in clinical and real-world settings where scanning time is limited.

Applications

Cognitive neuroscience

Behavioral correlates of brain fingerprints

Once FC fingerprints were established, the next question naturally arose concerning their functional and behavioral relevance [50]. Accordingly, multivariate statistical techniques, such as partial least squares, have been often employed to investigate the link between FC fingerprints and behavior in individuals. Key regions that were consistently identified as central for fingerprinting include the medial frontal and fronto-parietal network, default mode network, dorsal attention network, limbic, and visual networks [4], [5], [8], [22]. Fingerprint features within these regions have been correlated with age, gender, handedness, and clinical variables [22], as well as executive function performance [50]. In contrast, a recent study challenges the notion of a direct relationship between behavior and fingerprinting, showing that participant identification and behavioral prediction rely on largely distinct functional systems of the human connectome, including higher-order multimodal association cortices [51]. While the authors confirmed the functional relevance of fingerprinting connections—replicating previous findings that behavioral scores can be predicted from FCs in these circuits—they questioned the existence of a one-to-one mapping between function and fingerprints. Instead, they suggested that the variability enabling fingerprinting may arise from multiple sources, encompassing not only functional but also structural brain features.

Fingerprinting signatures of different cognitive states

Brain fingerprinting provides a unique perspective on individual differences in cognition. Recent studies have demonstrated that cognitive states and tasks significantly modulate brain fingerprinting accuracy, emphasizing the link between FCs and higher-order cognitive processes [16].

During sleep, brain fingerprinting capabilities are maintained, pointing at the sleep EEG power spectrum as a trait-like characteristic of the individual that remains unique from youth through old age [52].

Research using both fMRI and MEG has shown that individual identifiability improves when subjects engage in structured cognitive tasks compared to resting state [7], [16]. Specifically, controlled task paradigms enhance individual differentiation by modifying the spatial and temporal organization of functional connectivity patterns. Task-induced changes can be captured using the state-modulated identifiability measure

$$\mathbf{I}_{\Delta}^{\text{condition}}[p,q] = \frac{1}{N_S}\sum_{i=1}^{N_S}\left(\mathbf{I}_{p,q}^{\text{condition}}[i,i] - \frac{1}{N_S-1}\sum_{j\neq i}\mathbf{I}_{p,q}^{\text{condition}}[i,j]\right) \tag{10}$$

where $\mathbf{I}_{p,q}^{\text{condition}}$ represents the identifiability matrix for a specific pair of conditions p and q; i.e., instead of test/retest, one could assess identifiability between different types of tasks,

where rest could be one of them. Then $\mathbf{I}_{\Delta}^{\text{condition}}$ becomes a matrix itself for all possible condition pairs. For task-based identifiability, studies indicate that FC reorganizes dynamically based on-task constraints, leading to shifts in the dominant regions that contribute to fingerprinting [16]. Task-dependent modulation of brain fingerprints reveals that functional connectivity patterns shift dynamically depending on the cognitive context. This suggests that individual brain fingerprints are not static, but instead reflect an adaptive property of brain networks. As subjects engage in complex cognitive processes, regions such as the frontoparietal network and default mode network exhibit increased differentiation, improving the accuracy of identifiability. These insights highlight the importance of studying how brain fingerprints evolve across different cognitive states. Recent work also demonstrated the potential of naturalistic stimuli, such as movie-watching, to replace resting state [53].

Brain fingerprinting has also been applied to investigate pharmacologically induced cognitive states, termed *pharmacological fingerprinting* [54]. Pharmacological interventions provide a unique way to probe the flexibility of brain fingerprints. In particular, recent work on psilocybin has demonstrated that acute psychedelic states increase the intersubject dissimilarity of FCs, thereby enhancing fingerprint distinctiveness [54]. Under psilocybin, the FC pattern shifts from a frontoparietal-dominant fingerprint to one primarily localized in the default mode network, suggesting a drug-induced reconfiguration of cognitive processing.

Note that, following (10) with "condition" indicating drug-induced brain alterations, $\mathbf{I}_{p,q}^{\text{condition}}$ will denote the identifiability matrix computed under different pharmacological modulation p and q.

The increased differentiation observed in psychedelic states is believed to reflect a breakdown of hierarchical processing in the brain, leading to greater integration between sensory and higher-order networks [54]. These findings highlight the relevance of brain fingerprinting in cognitive neuroscience by demonstrating how neural identity is shaped by both task engagement and neuromodulatory influences.

A recent study explored how general anesthesia alters brain fingerprints by reducing the uniqueness of individual brain connectivity patterns. Using fMRI data from subjects under sevoflurane and propofol anesthesia, researchers found that individual brain networks become less self-similar and less distinguishable from each other [55]. The effect was strongest in transmodal cortical regions, such as the default mode and frontoparietal networks, which typically exhibit high interindividual variability. Additionally, anesthesia made human brain connectivity more similar to that of macaques, suggesting a regression to a more fundamental connectivity template. These findings highlight how loss of consciousness under anesthesia diminishes the distinctiveness of brain fingerprints, with potential implications for understanding neural individuality and cross-species connectivity.

Taking the data together, the study of brain fingerprinting in cognitive neuroscience underscores the adaptability of functional connectivity profiles. Whether through engagement in cognitive tasks or pharmacologically induced changes in consciousness, individual brain fingerprints provide valuable insights into the dynamic nature of neural identity. Future research in this field has the potential to revolutionize personalized medicine, paving the way to novel approaches to diagnose and treat cognitive and psychiatric disorders.

Clinical neuroscience

The previous sections have highlighted methodological advances in the extraction of brain fingerprints. The next step in this field is to refine our understanding of how connectome fingerprints can serve as biomarkers for neurological and neurodegenerative conditions.

One of the earliest approaches in this direction introduced clinical connectome fingerprinting [14] as a tool to test individual connectome similarity across healthy and pathological groups [Figure 3(a)]. This method extends conventional fingerprinting by including patient–control comparisons in the identifiability matrix [see gray blocks in Figure 3(a), top left]. By leveraging clinical fingerprinting scores and ICC metrics, researchers identified the most stable connectivity features across test/retest sessions, enabling finer discrimination between healthy individuals and those with neurological impairments [14].

Recent work has shown that FC profiles remain distinct even in pathological aging, albeit with notable reconfigurations as the disease progresses [Figure 3(b)]. For instance, in Alzheimer's disease (AD), FC shifts from higher-order cognitive functions to lower-order sensory-motor processes during the early stages, possibly reflecting compensatory mechanisms prior to overt cognitive decline [30]. Consistently, reduced identifiability in elderly populations has been linked to mild cognitive impairment, with lower fingerprinting accuracy predictive of disease progression.

In Parkinson's disease (PD), studies utilizing MEG-derived fingerprints have identified patient-specific rhythmic features [44], [56]. At the whole-brain level, patients are less identifiable than healthy controls, and this reduction scaled with motor impairment, suggesting a gradual erosion of fingerprint distinctiveness as the disease progresses. However, when focusing on specific brain regions in the somatomotor cortex, which showed the highest ICC values in the PD cohort, patients were more easily differentiated compared to controls. These findings highlight large-scale network functional dysregulation as a hallmark of neurodegeneration, while also pointing to region-specific fingerprints that could inform patient stratification and guide personalized neurostimulation therapies.

Preliminary research has also reported lower fingerprint stability in schizophrenia [47], with delayed stabilization and atypical individualization of connectomes during adolescence to adulthood, possibly linked to psychiatric vulnerability [47].

Finally, recent evidence suggests that patients with multiple sclerosis exhibit reduced identifiability, with specific functional connectivity alterations predictive of fatigue severity [Figure 3(c)] [17].

Together, these findings underscore the potential for brain fingerprinting to evolve into an objective tool to monitor disease burden and therapeutic response. However, this area of research is still at an early stage and translating these findings into actionable clinical decisions—such as diagnosis or treatment planning—remains challenging. From a technical perspective, the dependence of fingerprinting on the chosen methodology, preprocessing steps, and acquisition parameters,

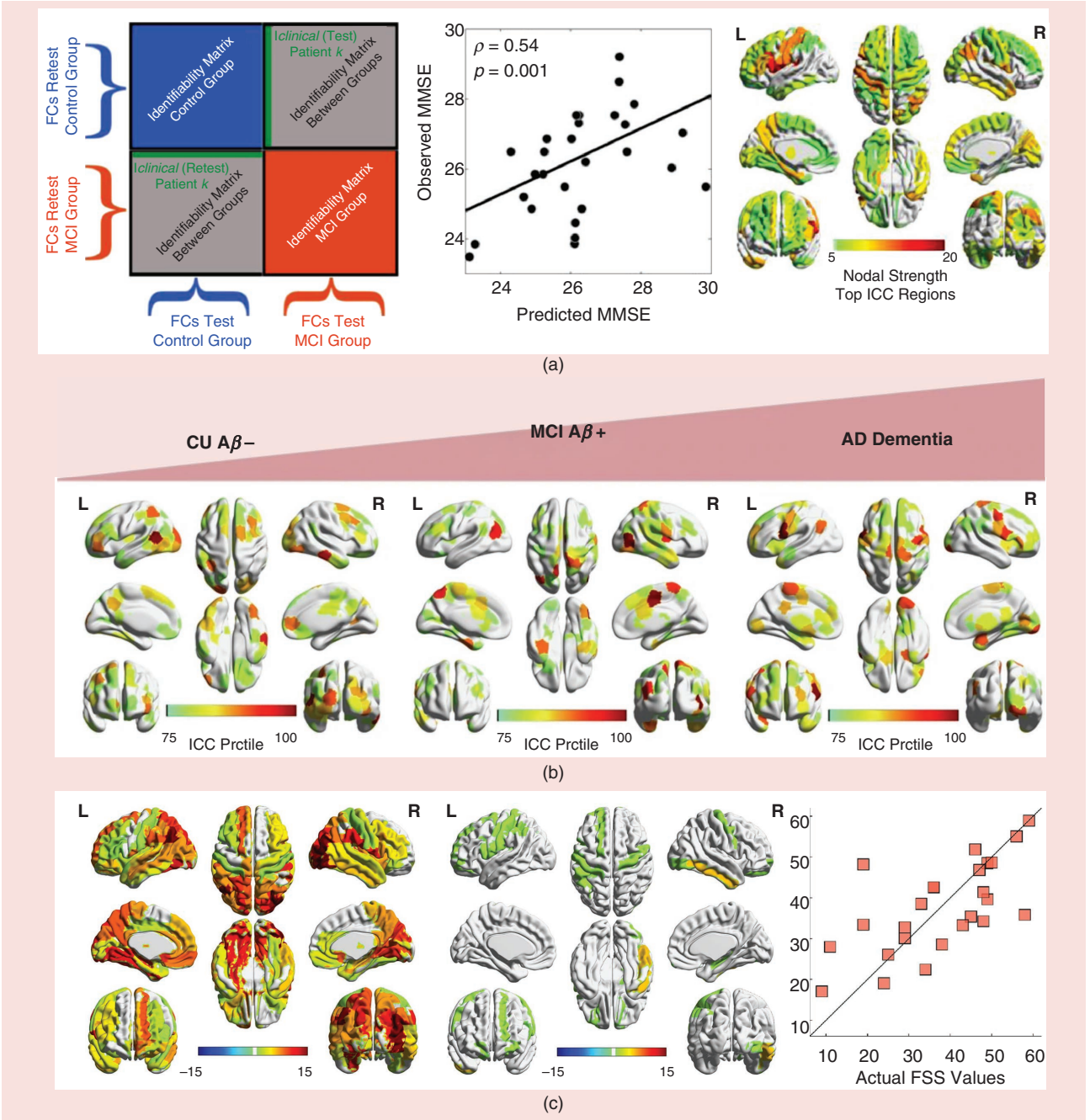

FIGURE 3. Overview of brain fingerprinting clinical applications. (a) Clinical connectome fingerprinting is used to detect individual connectome features from a clinical population with mild cognitive impairment (MCI), compared to healthy elderly. The block matrix is composed of "standard" identifiability matrices within the healthy and MCI group (red and blue blocks, respectively), plus the off-diagonal block elements that encode the individual similarity between groups (gray blocks). For each patient, I*clinical* (green row and column) can then be defined as the average similarity of their individual connectome with the healthy control population. This framework is then used to predict behavioral scores, such as the mini-mental score examination (MMSE). Top brain regions for prediction are identified as the highest ICC values (adapted from [14]). (b) FC profiles showed to also remain unique across the pathological evolution of aging toward Alzheimer's disease (AD), but with a reconfiguration of the brain fingerprint, highlighted by the different brain regions of ICC peaks when going from cognitively unimpaired (CU) amyloid β-negative (A$\beta-$), to MCI amyloid β-positive (A$\beta+$), to AD (adapted from [30]). (c) Clinical connectome fingerprint analysis extracts subject-specific connectome features also in multiple sclerosis, but with lower ICC values for patients (right brain plot) versus controls (left). The identifiability parameters are able to predict multiple sclerosis-related fatigue measured with the fatigue severity scale (FSS) (adapted from [17]).

limit reproducibility and hinder the development of standardized clinical tools. From an interpretative standpoint, much remains to be understood regarding the alteration of identifiability patterns in the presence of disease. On the one hand, fingerprinting alterations appear disease-specific and not generalizable across clinical conditions. For instance, idiosyncratic FC patterns in autism spectrum disorder [57] may increase intersubject variability and ameliorate fingerprinting performances, in contrast to the reductions seen in AD or PD. On the other hand, the reduction of identifiability common to many of the mentioned disorders might find different explanations. First, convergence toward a common pathological pattern of brain alteration could reduce intersubject variability, effectively placing patients on a shared disease trajectory. Second, increased intrasubject variability during disease progression—particularly in longitudinal test/retest sessions spaced months or years apart—may diminish identifiability, even when within-session fingerprints remain preserved, as shown in AD [30]. Third, specific clinical conditions may require focusing on specific brain patterns of higher identifiability, that differ from those in healthy subjects due to a reconfiguration of the brain fingerprint, as discussed for PD and AD.

Conclusion

In this review, we highlighted brain fingerprinting methodologies that combine signal processing and machine learning techniques, while maintaining high interpretability. In essence, interindividual variability in FC is exploited for phenotyping in cognitive neuroscience, as well as diagnosis and prognosis in clinical neuroscience, potentially guiding targeted therapeutic interventions as part of precision medicine in neurology and psychiatry.

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