Virtual connectomic datasets in dementia and Alzheimer's Disease using whole-brain network dynamics modelling

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Abstract

Large neuroimaging datasets, including information about structural (SC) and functional connectivity (FC), play an increasingly important role in clinical research, where they guide the design of algorithms for automated stratification, diagnosis or prediction. A major obstacle is, however, the problem of missing features (e.g., lack of concurrent DTI SC and resting-state fMRI FC measurements for many of the subjects).

We propose here to address the missing connectivity features problem by introducing strategies based on computational whole-brain network modeling. Using the ADNI dataset for proof-of-concept, we demonstrate the feasibility of virtual data completion (i.e., inferring "virtual FC" from empirical SC or "virtual SC" from empirical FC), by using self-consistent simulations of nonlinear brain network models, superior to simpler linear models. Furthermore, by performing machine learning classification of control and patient subjects, we show that algorithms trained on virtual connectomes achieve discrimination performance comparable to when trained on actual empirical data; similarly, algorithms trained on virtual connectomes can be used to successfully classify novel empirical connectomes. Nonlinear completion algorithms can be combined and reiterated to generate realistic surrogate connectivity matrices in arbitrarily large number, opening the way to the generation of virtual connectomic datasets with network connectivity information equivalent to the one of the original data.

Introduction

Despite decades of massive investment in Alzheimer's disease (AD) research and the daunting literature on the topic, the partial and, sometimes contradictory nature of the reported results (World Alzheimer Report 2018) still prevents a complete understanding of the factors governing the progression of the disease (Braak & Braak, 1991; Braak et al., 2006; Komarova & Thalhauser, 2011; Henstridge et al., 2019) or of the diversity of cognitive deficits observed in different subjects (Iacono et al., 2009; Mungas et al., 2010; Allen et al., 2016). In this context, datasets that compile rich and diverse genetic, biomolecular, cognitive, and neuroimaging (structural and functional) features for a large number of patients are playing an increasingly important role (Rathore et al., 2017; Iddi et al., 2019). Example applications include: the early diagnosis and prognosis by using MRI images (Dennis & Thompson, 2014; Chiesa et al., 2017; De Vos et al., 2018); the use of machine learning for automated patient classification (Cuingnet et al., 2011; Zhang et al., 2012; Moore et al., 2019) or prediction of the conversion from early stages to fully developed AD (Rombouts et al., 2005; Moradi et al., 2015; Casanova et al., 2018); the extraction of decision networks based on the combination of semantic knowledge bases and data mining of the literature (Sanchez et al., 2011; Kodamullil et al., 2015; Iyappan et al., 2016).

Among the factors contributing to the performance of prediction and inference approaches in AD –and, more in general, other neurological or psychiatric diseases– are not only the large size of datasets but also the multiplicity of features jointly available for each patient. Indeed, one can take advantage not only of the complementary information that different features could bring but also capitalize on possible synergies arising from their simultaneous knowledge (Wang et al., 2015; Zimmermann et al., 2016; Iddi et al., 2019). Unfortunately, even gold standard publicly available datasets in AD, such as the datasets released by the Alzheimer's Disease Neuroimaging Initiative (ADNI) consortium (Wyman et al., 2013; Beckett et al., 2015; Weiner et al., 2017), have severe limitations. Indeed, if they include neuroimaging features of different types –structural DTI and functional MRI– these features are simultaneously available for only a substantial minority of the subjects in the dataset (i.e., the feature coverage is not uniform over the dataset). Furthermore, if the number of subjects included is relatively large (hundreds of subjects), it still is too small to properly qualify as "big data". Finally, although we focus here on AD as an important application case, these aforementioned issues are widespread and may affect in principle any other connectomic dataset gathered for data mining intents.

Here we propose a new solution aiming at relieving these problems of partially missing features and limited sample size. To do so, we build on the quickly maturating technology of mean-field whole-brain network modeling (see Deco et al., 2011 for review). Importantly, the use of whole-brain modeling is greatly facilitated by the existence of dedicated neuroinformatic platforms –such as "The Virtual Brain" (TVB; Sanz-Leon et al., 2013, 2015; Woodman et al., 2014)– and data pre-processing pipelines (Schirner et al., 2015; Proix et al., 2016), enabling brain model personalization and clinical translation (Jirsa et al., 2017; Proix et al., 2017). Computational modeling provides a natural bridge between structural and functional connectivity, the latter emerging as the manifestation of underlying dynamical states, constrained but not entirely determined by the underlying anatomy (Ghosh et al., 2008; Kirst et al., 2016). Theoretical work has shown that average functional connectivity properties in the resting-state can be accounted for by the spontaneous collective activity of brain networks informed by empirical structural connectivity (SC) when the system is tuned to operate slightly below a critical point of instability (Deco et al., 2011, 2012). Based on this finding, simulations of a model constructed from empirical DTI connectomes and then tuned to a suitable slightly sub-critical dynamic working point are expected to provide a good rendering of resting-state functional connectivity (FC). It thus becomes possible to complete the missing information in a dataset about BOLD fMRI FC by running a TVB simulation in the right regime, embedding the available empirical DTI SC (*SC-to-FC completion*). Analogously, algorithmic procedures based on mean-field modeling steps (Gilson et al., 2016; 2018) can be used to address the inverse problem of inferring SC from FC (*FC-to-SC completion*). In this work, we provide initial proofs-of-concept of data completion using TVB-technologies, using them to "fill gaps" in the ADNI neuroimaging dataset, generating the missing connectivity SC (or FC) connectivity matrices from the available FC (or SC) ones.

Furthermore, by combining completion procedures – to map, e.g., from an empirical SC (or FC) to a virtual FC (or SC) and then, yet, to a "twice virtual" SC (or FC)– we can generate for each given empirical connectome a virtual dual replacement. We show then that pairs of real and virtual dual connectivity matrices display highly correlated network topology features, such as node-level strengths or clustering and centrality coefficients (Bullmore & Sporns, 2009). We demonstrate along the example of a relevant classification task (stratification of mild cognitive impairment (MCI) or AD patients from control subjects) that similar performance can be reached using machine learning algorithms trained on virtual or empirical connectomes. Furthermore, empirical connectomes can be correctly categorized by classifiers trained uniquely on virtual duals.

To conclude, we provide systematic recipes for generating realistic surrogate connectomic data via data-constrained mean-field models. We show that the information that we can extract from computationally inferred

connectivity matrices are largely equivalent to the one carried by the original empirical data. This opens the way to the design and sharing of veritable "virtual cohorts" data, ready for machine-learning applications in clinics, that could complement actual empirical datasets –facilitating learning through "data augmentation" (Yaeger et al., 197; Taylor & Nitschke, 2018)– or, even, potentially, replace them, e.g. when the sharing of real data across centers is restricted due to byzantine regulation issues.

Results

ADNI connectomic data have gaps

In the framework of this study, we chose to focus on one of the first and most popular available datasets in AD research, including a substantial amount of structural and functional connectomic information, i.e. the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). ADNI is impressive for the variety of features it aimed at systematically gathering (Figure 1A). Importantly, based on the T1, DTI and resting-state (rs) BOLD fMRI images available through the ADNI data-sets, state-of-the-art processing pipelines can be used to extract subject-specific Structural and resting-state Functional Connectomes, compiled into connectivity matrices adapted to the brain parcellation of choice (Figure 1B, see *Materials and Methods* for details).

We had access to an empirical of 244 overall subjects (119 labeled as "MCI", 51 as "AD", in addition to 74 control subjects, see *Materials and Methods*) for which MRI data had been gathered. We could extract an FC matrix for 168 subjects (starting from rsfMRI) and a SC matrix (starting from DTI) for 88 subjects. However, only for a minority of 12 subjects rsBOLD and DTI information were both available. In a majority of cases, either DTI or rsBOLD were missing (Figure 1C). This reduced number of "complete" subjects constitutes a serious challenge to attempts of automatedly categorize them through machine learning or inference approaches capitalizing on both SC and FC features simultaneously. As a matter of fact, the total numbers of AD- and MCI-labeled subjects in this complete subset decreased respectively to just 2 and 4, against 6 controls. In these conditions, the development of effective data completion strategies would be an important asset toward the development of classifier schemes exploiting FC/SC synergies. Therefore, approaches to "fill gaps" (completion) and, possibly, even artificially boosting sample size (augmentation) are veritably needed.

Linking SC and resting-state FC via computational modeling

As previously mentioned, FC and SC are related only indirectly through the rich non-linear dynamics supported by brain networks (Ghosh et al., 2008; Deco et al., 2011; Kirst et al., 2016). Mean-field modeling of large-scale brain networks has emerged initially as the key tool to predict the emergent dynamic patterns of resting-state FC, from spontaneous dynamics constrained by SC (Ghosh et al., 2008). It is thus natural to propose the use of model-based solutions to perform data-completion, which, in both the SC-to-FC and FC-to-SC directions, requires to capture the inter-relation between the two as mediated by dynamics.

Large-scale mean-field brain network models are specified by: i) a parcellation of cortical and subcortical brain areas; ii) a co-registered input SC matrix in the same parcellation; iii) a forward solutions linking source and sensor space; iv) a neuronal mass model, describing the non-linear dynamics of the regions at each of the nodes of the SC matrix; v) a choice of a few global parameters (e.g. scale of strength of inter-regional connectivity or speed of signal propagation along fiber tracts); vi) an external input given to the different regions, that, in the simplest case, corresponds to simple white noise uncorrelated across each of the different sites and of homogeneous strength. The Virtual Brain enables the complete workflow from brain images to simulation (TVB; Sanz-Leon et al., 2013, 2015). Personalization is accomplished by the subject-specific structural skeleton – ingredients (i) through (iv)–, which has been demonstrated to be individually predictive (Proix et al 2017; Melozzi et al 2019). Simulations of the model can be run to generate surrogate BOLD time-series of arbitrary length (see *Materials and Methods* for details) and the associated simulated resting-state FC, time-averaged (static FC) or even time-resolved (FC dynamics or dFC, Hansen et al., 2015). The thus obtained simulated FC will depend on the chosen global parameters, setting the *dynamic working point* of the model. The model dynamics will eventually switch between alternative dynamical regimes when its global control parameters cross specific critical points. Tuning global parameters will thus uniquely determine, in which regime the model operates. Mean-field large scale models constrained by empirical SC tend to generate simulated resting-state FC that best matches empirical observations when the dynamic working point of the model lies in the proximity of a model's critical point (Deco et al., 2011; Deco et al., 2013; Hansen et al., 2015; Triebkorn et al., 2020).

We here chose one of the simplest possible whole-brain network model designs, which emphasizes activity-based network organization (as opposed to reorganization due to synchronization) and thus ignores inter-regional

propagation delays. This approach is frequently used in the literature (e.g., Deco et al., 2013; Hansen et al., 2015; Aerts et al., 2018) and has the advantage of avoiding the need for complex delay differential equation integration schemes (see *Discussion* for more details). Activation-based approaches adopt particularly simple neural mass models such as the reduced Wong-Wang model (Deco et al., 2013), in which the dynamics of an isolated brain region is approximated by either one of two possible steady states, one "down state" at low firing rate and an "up state" at high firing rate, a feature initially meant to mimic bi-stability in working memory or decision making (Wong & Wang, 2006). By varying *G* the model will switch from a low-coupling regime, in which all regional activations are low to a high-coupling regime, in which all regional activations are high, passing through an intermediate range, in which both regimes can exist in a multistable manner and regions display spatially and temporally heterogeneous activations (a changing mix of high and low firing rates). The best fit between simulated and empirical FC occurs slightly before the critical rate instability, at which modes of activity with low firing rate disappear (Deco et al., 2013).

As alternatives to the just described *non-linear mean-field models* (MFMs) of resting-state brain dynamics, simpler *stochastic linear models* (SLMs) have also been considered (Goñi et al., 2014; Messé et al., 2014; Saggio et al., 2016). In these models, the activity of each region is modeled as a stochastic process (linear, in contrast to the non-linear neural mass dynamics of conventional MFMs), biased by the fluctuations of the other regions weighted by the SC connectome (see *Materials and Methods*). SLMs have also two different regimes. In the first regime, the activities of all regions converge to a fixed-point of constant mean fluctuating activities, while, in the second, regional activities diverge with exponential growth. Once again, the best fit between the simulated and the empirical resting-state FCs is observed when tuning the model parameters slightly below the critical point (Hansen et al., 2015; Saggio et al., 2016).

MFMs and SLMs provide thus two natural ways to generate simulated resting-state FCs, depending on the chosen dynamic regime, starting from a selected SC. Strategies have also been devised to approximately solve the inverse problem of determining which SC matrix should be used as input to a model in order to give rise to a simulated FC matching a specific, pre-determined target matrix. For the SLM, a simple analytic solution to the inverse problem exists (Saggio et al., 2016). For MFMs, inverse problems have not been studied with the same level of rigor, but algorithms have been introduced that iteratively adjust the weights of the SC matrix currently embedded in the model to improve the fit between simulated and target FCs (Gilson et al., 2016; 2018). We will show later that these "effective connectivity" algorithms have the potential to cope with the actual problem of MFM inversion.

As linear approaches are significantly faster than non-linear approaches, it is important to study their performance alongside nonlinear approaches to confirm the actual justification of the use of more complicated algorithms. We will see that, indeed, non-linear methods are superior for the data completion applications we are interested in.

Model-driven data completion

Figure 2 summarizes many of the modeling operations described in the previous section framing them in the specific context of connectomic data completion. MRI data can be used to generate empirical SC matrices SC_{emp} (from DTI) or FC_{emp} (from rs fMRI BOLD). By embedding the empirical matrix SC_{emp} into a non-linear MFM or a linear SLM, it is possible to compute surrogate FC matrices (Figure 2A, upward arrows), denoted, respectively, FC_{MFM} and FC_{SLM}. The MFM and SLM global parameters are suitably tuned (slightly subcritical) then FC_{MFM} and FC_{SLM} will be maximally similar to the empirical FC_{emp} (dynamic working point tuning, represented by dashed grey arrows in Figure 2A). Starting from the empirical matrix FC_{emp}, one can then infer surrogate SC matrices (Figure 2A, downward arrows), either by using a linear theory –developed by Saggio et al. (2016)– to compute a surrogate SC_{SLM}; or by exploiting non-linear effective connectivity algorithm –generalized from Gilson et al. (2016; 2018)– to infer a surrogate SC_{MFM} starting from a random initial guess (see later section).

When connectomic data are incomplete (only SC_{emp} or only FC_{emp} are available, but not both simultaneously), computational simulation or inference procedures can be used to fill these gaps: by using FC_{MFM} or FC_{SLM} as virtual replacements for a missing FC_{emp} (Figure 2B); or by using SC_{MFM} or SC_{SLM} as virtual replacements for a missing SC_{emp} (Figure 2C). The quality of the model-generated virtual SCs and FCs can be assessed by comparing them with the actual empirical counterparts for the small subset of subjects for which both SC_{emp} and FC_{emp} are simultaneously available. Optimizing the quality of the virtually completed matrices on the subset of "SC_{emp}+FC_{emp}" subjects, also allows extrapolating target criteria for identifying when the model is operating a suitable dynamic working point, that can be evaluated solely based on simulated dynamics when a fitting target matrix is missing and thus fitting quality cannot be explicitly measured (cf. Figures 3 and 4). We can thus translate these criteria into precise algorithmic procedures that inform linear or non-linear SC-to-FC and FC-to-SC completion (see Tables 1-2 and S1-S2).

We now, provide more details on implementation and performance for each of the four mentioned types of data completion.

Linear SC-to-FC completion is not viable

In linear SC-to-FC completion, a simple SLM (see *Materials and Methods*) is constructed based on the available SC_{emp} and its direct simulations or even, in a much faster manner, analytical formulas deriving from the model's theory are used to generate the associated virtual Pearson correlation matrix FC_{SLM} (Figure S1). In this stochastic linear modeling scheme, once the driving noise strength is arbitrarily chosen and fixed and the input connectome SC_{emp} is specified, there remains a single parameter to adjust, the global scale of long-range connectivity strength G. Figure S1A shows a systematic exploration, performed on subjects from the "SC_{emp}+FC_{emp}" subset, of how the completion quality depends on tuning this parameter G. As shown by the main plot in Figure S1A for a representative subject, increasing G the correlation between the empirical FC_{emp} and the simulated FC_{SLM}, derived here from direct SLM simulations, initially grows to peak in proximity of a critical value G^*. The correlation then drops dramatically when further increasing G beyond the critical point G^*.

The exact value of G^* depends on the specific personalized SC_{emp} connectome embedded into the SLM and is therefore different for each subject. The small boxplot inset in Figure S1A gives the distribution of the personalized G^* over all the subjects in the "SC_{emp}+FC_{emp}" subset. However, when performing linear FC completion because BOLD data and FC_{emp} are missing, the exact location of the fitting optimum cannot be determined. To perform linear SC-to-FC completion for the ADNI subjects with missing BOLD we chose to always use a common prescribed value $G^*_{ref} = 0.83$, set to be equal to the median of the personalized G^* over the "SC_{emp}+FC_{emp}" subset of ADNI subjects.

Once a G^*_{ref} value and a noise strength are set, the linear completion can be further sped-up by the fact that the covariance matrix FC_{SLM} for these frozen parameters can be analytically evaluated, as discussed in Saggio et al. (2016). Therefore, one can directly apply the SLM analytical formulas (see *Material and Methods*) on the available SC_{emp} as input, without the need for performing direct simulations to generate surrogate BOLD first. Figures S1B-C analyze the expected performance of this "simulation-less" procedure, as benchmarked by applying it on the "SC_{emp}+FC_{emp}" subset. The boxplot in S1B reports a median Pearson correlation between the linear virtual FC_{SLM} and the actual empirical FC_{emp} close to ~0.24. Panel S1C indicates then the percent loss in correlation that has been caused by using the common value G^*_{ref} and the analytical formula to evaluate the linear virtual FC_{SLM} rather than direct simulations at the actual personalized optimum G^* for each of the "SC_{emp}+FC_{emp}" subjects. The median quality loss is approximately 0.5%, indicating that the lack of personalized tuning of the SLM working point is only a minor issue and that is acceptable to speed-up completion by relying on analytical evaluations.

Table S1 provides a pseudo-code for the linear SC-to-FC completion procedure (see *Materials and Methods* for all details). Linear SC-to-FC completions for the DTI-only subjects in the considered ADNI dataset can be downloaded as Supplementary File S1. To test whether the median Pearson correlation of ~0.24 between the linear virtual FC_{SLM} and the actual empirical FC_{emp} is "good enough" for the use of a simple linear completion procedure, we use the SC_{emp} connectome itself as a substitute for the missing FC_{emp} rather than using a linear completion algorithm. As a matter of fact, it is known that the empirical SCs and FCs are already strongly related (Hagmann et al., 2008) and it may be that an even faster strategy for completion would be simply to use the "other connectome". We thus computed the percent improvement in rendering FC_{emp} via FC_{SLM} for subjects in the "SC_{emp}+FC_{emp}" subset. As shown in Figure S2A, the use of FC_{SLM} resulted systematically in a *worse* performance (median drop of ~15%) in reproducing the actual FC_{emp} than using the other available connectome SC_{emp}. Therefore, the linear procedure here discussed cannot be considered as a useful strategy for SC-to-FC completion.

Non-linear SC-to-FC completion is viable

In non-linear SC-to-FC completion, a more complex MFM (see *Materials and Methods*) is constructed based on the available SC_{emp} and is simulated to generate surrogate BOLD data and the associated Pearson correlation matrix FC_{MFM} (Figure 3). Non-linear mechanistic MFM models are more compliant with neurophysiology than the phenomenological SLMs. Furthermore, because of their non-linearities, they are potentially able to capture complex emergent collective dynamics resulting in non-trivial dFC (which SLMs cannot render, cf. Hansen et al., 2015). However, MFMs have also more parameters and are computationally costlier to simulate than SLMs.

We chose here to limit ourselves to MFMs based on a reduced Wong-Wang regional dynamics (see *Materials and Methods* for model equations), which has previously been used to successfully reproduce rsFC (Deco et al., 2013) and dFC (Hansen et al., 2015) starting from empirical SC, despite its relative simplicity with respect to other possible neural masses implemented in the TVB platform. In addition to the global scale of long-range

connectivity strength G, the MFM model dynamics depend also on regional dynamics parameters. In Figure 3, we froze all local parameters but the NMDA decay time-constant τ, since they affected the dynamic behavior of the model less than the other control parameters and, in particular, did not alter qualitatively the repertoire of accessible dynamical regimes (compare Figure 3A with Figure S3). The simulated collective dynamics and the resulting non-linear virtual FC_{MFM} will depend on the choice of the free control parameters G and τ. In Figure 3A, we have explored the dependency of the correlation between FC_{MFM} and the actual empirical FC_{emp} as a function of G and τ achievable over the subjects in the "SC_{emp}+FC_{emp}" subset. As evident in figure 3A, this dependence is non-monotonic and the best-fitting qualities are concentrated in a narrow concave stripe across the G/τ plane. Panels 3B and 3C report zoom of Figure 3A into increasingly smaller regions, revealing an extended zone of high fitting quality which some absolute optimum parameters G^* and τ^* (here $G^* = \sim 1.5$ and $\tau^* = 25$).

Remarkably, this best-fitting quality zone on the G/τ plane is associated as well to other properties that can be evaluated just based on the simulated dynamics (and, therefore even when the actual target FC_{emp} is unknown and missing). We found that the best fit quality systematically occurs in a region where three criteria are jointly met (Figures 3D-F).

First, there is a mixture of "ignited" regions with large activation and of not yet ignited regions with a weaker firing rate (*spatial heterogeneity*, Figure 3D). Conversely, when moving out of the best-fitting zone, the activity becomes more spatially homogeneous, either with all regions stable at low (for $G <<< G^*$) or high (for $G >>> G^*$) firing rates.

Second, the time-averaged FC_{MFM} has a complex modular organization between order and disorder, associated to high average clustering coefficient, in contrast with the absence of clustering observed for $G <<< G^*$ or $G >>> G^*$ (*structured FC*, Figure 3E).

Third, the simulated collective dynamics give rise to meta-stability of FC along time, i.e. to a non-trivially structured dFC, which alternates between "knots" of transiently slowed-down FC network reconfiguration and "leaps" of accelerated reconfigurations. Such non-triviality of dFC can be detected by the inspection of the so-called dFC matrix (Hansen et al., 2015; Battaglia et al., 2020; Lombardo et al., 2020), representing the similarity between FC matrices computed at different time-windows (see *Materials and Methods*). In this dFC matrix analysis, dFC "knots" are visualized as blocks with high inter-FC correlations, while dFC "leaps" give rise to stripes of low inter-FC correlation. The prominence of the block structure of the dFC matrix can be measured by the dFC clustering coefficient (see *Material and Methods*), higher when the dFC matrix includes more evident knots. The dFC clustering coefficient is higher in the best fit zone, while it drops moving outside it toward $G <<< G^*$ or $G >>> G^*$ (*structured dFC*, Figure 3F).

By scanning the G/τ plane in search of a zone with simultaneous spatial heterogeneity of activations, structured FC and structured dFC, the MFM model parameters can be tuned to bring it in a zone invariantly resulting in relatively higher fitting quality. Figure 3G shows the analysis of the expected performance of this procedure, as benchmarked by applying it on the "SC_{emp}+FC_{emp}" subset. We measured a median Pearson correlation between the non-linear virtual FC_{MFM} and the actual empirical FC_{emp} close to ~0.32.

Table 1 provides a compact pseudo-code for the non-linear SC-to-FC completion procedure (see *Materials and Methods* for all details). Non-linear SC-to-FC completions for the DTI-only subjects in the considered ADNI dataset can be downloaded as Supplementary File S2.

The value of correlation with FC_{emp} achieved by FC_{MFM} is larger than the one by FC_{SLM}. Nevertheless, it remains necessary to check that it constitutes an improvement on the trivial strategy over taking the "other connectome" as substitute (i.e. taking FC to be identical to SC_{emp}). In Figure S2A, we show that this is indeed the case, unlike for linear SC-to-FC completion. The procedure sketched in Table S1 led to a median improvement on using the "other connectome" approaching ~20%, that can go as high as +50% in some cases. Therefore, nonlinear SC-to-FC computational generation provides a viable strategy for data completion.

Linear FC-to-SC completion is not viable

In linear FC-to-SC completion, we use once again the analytic theory derived for the SLM (Saggio et al., 2016) to deterministically compute a surrogate SC_{SLM} as a function of the available FC_{emp} or, more precisely, of the resting-state $BOLD_{emp}$ time-series used to derive FC_{emp}. In this scheme, the linear virtual SC_{SLM} is indeed taken to be directly proportional to the *inverse covariance* of the BOLD time-series (see *Materials and Methods*). The proportionality constant would depend on the free parameters chosen for the SLM, serving as a link between FC and SC. Here we set arbitrarily this constant to the unit value.

Figure S4 shows the analysis of the expected performance of this procedure, as benchmarked by applying it on the "SC_{emp}+FC_{emp}" subset. We measured a median Pearson correlation between the linear virtual SC_{SLM} and the actual empirical SC_{emp} close to ~0.22.

Table S2 provides a pseudo-code for the linear FC-to-SC completion procedure (see *Materials and Methods* for all details). Linear FC-to-SC completions for the BOLD-only subjects in the considered ADNI dataset can be downloaded as Supplementary File S3.

As for SC-to-FC completions, we confirmed if the performance reached by linear FC-to-SC completion is superior to the one that is obtainable through the trivial strategy of using "the other connectome" (in this case, the available FC_{emp}). In Figure S2B, we show that using SC_{SLM} rather than FC_{emp} as an ersatz for SC_{emp} generally leads to a drop in rendering quality, with a median value of approximately -20%. Therefore, as in the case of SC-to-FC completion, linear procedures do not constitute a viable strategy for data completion.

Non-linear FC-to-SC completion is viable

Non-linear FC-to-SC completion consists in the inference of a SC_{MFM} matrix that, used as input to an MFM, produces as output a simulated FC* matrix highly correlated with the available empirical FC_{emp} (Figure 4). This non-linear inverse problem is more sophisticated than linear FC-to-SC completion, because, for the MFM a theory providing an explicit formal link between input structural connectome (SC*) and output functional connectome (FC*) is not available, unlike for the SLM. Note indeed that MFMs, at the best-fitting dynamic working point, give rise not just to a single dynamical mode, but to a multiplicity of them (Deco & Jirsa 2012; Hansen et al., 2015; Golos et al., 2015) and that each of them may be associated, in general, to a different state-specific FC (Battaglia et al., 2012; Hansen et al., 2015; Kirst et al., 2016) so that the final static FC* results from averaging over a mixture of different states sampled in stochastic proportions. Therefore, to derive the FC* associated with a given input SC*, it is necessary to run explicit MFM simulations.

Gilson et al. (2016; 2018) have introduced iterative optimization procedures aiming at updating a current guess for the input SC* to a model in order to improve the match between the model output FC* and a target FC_{emp}. In this "effective connectivity" procedure –named as such by Gilson and coworkers, even if different from effective connectivity measures defined more typically in terms of statistical causality metrics (Valdes-Sosa et al., 2011)– connectome weights are iteratively and selectively adjusted as a function of the difference occurring between the current FC* and the target FC_{emp}. Such optimization leads to infer refined connectomes, that, with respect to empirical DTI SC matrix, may display non-symmetric connections (distinguishing thus between "feeder" and "receiver" regions as in Gilson et al., 2016) or enhanced inter-hemispheric connections, usually under-estimated by DTI (as in Gilson et al., 2018). Here we use a similar algorithm to learn a suitable non-linear virtual SC_{MFM}.

The initial $SC^*_{(0)}$ is taken to be a matrix with fully random entries. An MFM embedding such $SC^*_{(0)}$ is built and simulations are run to generate an output $FC^*_{(0)}$ which is compared to the target FC_{emp} of the subject for which FC-to-SC completion must be performed. The used $SC^*_{(0)}$ is then modified into a different $SC^*_{(1)} = SC^*_{(0)} + \lambda\Delta FC_{(0)}$ matrix, by performing a small update step in the direction of the gradient defined by the difference $\Delta FC_{(0)} = FC_{emp} - FC^*_{(0)}$. A new simulation is then run to produce a new $FC_{(1)}$. The produce is repeated generating new $SC_{(i)} = SC_{(i-1)} + \lambda\Delta FC_{(i-1)}$ until when the difference between $FC_{(i)}$ and the target FC_{emp} becomes smaller than a specified tolerance, i.e. $|\Delta FC_{(i)}| < \varepsilon$. The last generation $SC_{(i)}$ is then taken as non-linear virtual surrogate SC_{MFM} (see *Materials and Methods* for details).

Figure 4A provides an illustration of the nonlinear FC-to-SC completion when applied to subjects in the "SC_{emp}+FC_{emp}" subset. In the first step, the matrix $SC^*_{(0)}$ is random and there is no correlation between the output $FC^*_{(0)}$ and FC_{emp}. Advancing through the iterations, $SC^*_{(k)}$ develops gradually more complex internal structures and correspondingly, the correlation between $FC^*_{(k)}$ and FC_{emp} increases until when it reaches the desired quality threshold, here set to $CC_{target} = 0.7$. This threshold quality is usually reached after ~1500 iterations. In the "SC_{emp}+FC_{emp}" subset we can even take advantage of the availability of the actual SC_{emp} to quantify as well the convergence of $SC^*_{(k)}$ toward SC_{emp}. Figure 4A shows that advancing through the iterations, the correlation between $SC^*_{(k)}$ and SC_{emp} improves as well. The expected quality of reconstruction, as estimated from results on the "SC_{emp}+FC_{emp}" subset is reported in Figure 4B and amounts to an expected correlation between SC_{MFM} and SC_{emp} of ~0.31.

Table 2 provides a compact pseudo-code for the non-linear FC-to-SC completion procedure (see *Materials and Methods* for all details). Non-linear FC-to-SC completions for the BOLD-only subjects in the considered ADNI dataset can be downloaded as Supplementary File S4.

As for SC-to-FC completion, we confirmed if the nonlinear FC-to-SC completion SC_{MFM} does provide a superior reconstruction of SC_{emp} than the trivial alternative offered by just taking the "other connectome" (the available FC_{emp}). As shown in Figure S2B, the use of nonlinear FC-to-SC completion led to a median improvement on the order of ~15%. Therefore, nonlinear FC-to-SC computational generation provides a viable strategy for data completion, although not yet as efficient as SC-to-FC completion.

We note that non-linear FC-to-SC completion, as for non-linear SC-to-FC completion, is a non- deterministic procedure, meaning that a different SC_{MFM} is generated depending on the starting initial condition $SC^*_{(0)}$.

However, the different non-linear virtual surrogates lie at distances from the common actual ground truth SC_{emp} which are tightly concentrated around the median correlation. As revealed by Figure 4C, the reported correlations between SC_{MFM} and SC_{emp} were within a narrow interval of ±2.5% of the relative difference from the median distance for all the tested random initial conditions (30 per subject, see *Materials and Methods*), showing that the expected performance is poorly affected by the initial conditions. This stochastic aspect of the non-linear completion algorithm is going to allow us to generate not just one but arbitrarily many completions, starting from each available empirical connectivity matrix (see later section).

Virtual and bi-virtual duals and the self-consistency of data completion

MFMs have thus the capacity to bridge from SC to FC or from FC to SC in a way that goes beyond capturing the mere similarity between the empirical SC_{emp} and FC_{emp} connectomes. When using these models for data completion, the input matrix is always an empirical matrix (SC_{emp} or FC_{emp}) and the output a surrogate virtual matrix (respectively, FC_{virt} or SC_{virt}, where the index "virt" refers generally to any completion algorithm, i.e. either using the SLM or the MFM models). However, the algorithms presented in Tables 1-2 and S1-S2 can still be applied even when the input connectivity matrix is *already* a virtual matrix. In this case, the input could be surrogate matrices (SC_{virt} or FC_{virt}) from data completion and the output would be *bi-virtual* (respectively, FC_{bivirt} or SC_{bivirt}), i.e. twice virtual, since, to obtain them starting from an empirical input connectome, two different model-based procedures have to be chained. The final result of passing an original empirical connectome through two chained completion procedures is then a bi-virtual surrogate matrix of the same type (structural or functional) of the initially fed connectome. In other words, SC_{emp} is mapped to a SC_{bivirt} (passing through an intermediate FC_{virt} step) and FC_{emp} is mapped to an FC_{bivirt} (passing through an intermediate SC_{virt} step).

The virtual and bivirtual matrices obtained by operations of data-completion can be seen as a set of connectomes *dual* to the original real connectome. In mathematics, one often speaks of "duality" relations when two alternative spaces are put into relation by an element-to-element structure-preserving mapping. Here, one could reinterpret our algorithmic procedures for SC-to-FC or FC-to-SC completion as mapping between alternative "spaces" in which to describe the inter-relations between the connectomes of different subjects. Although our definition of duality is not as rigorous as in more mathematical contexts (as in the case, e.g., of linear algebra dual or bidual spaces; or in graph theory, where duality refers to node-to-link transformations), we will see that dissimilarities or similarities between the personalized connectomes of different subjects are substantially preserved by the application of completion procedure that maps an original space of empirical connectomes into a dual space of virtual connectomes. In other way, the information carried by a set of connectomes and by the set of their dual counterparts is, at least in part, equivalent (cf. Figures 5, 6, and *Discussion*). In this view, the first "dualization" operation would map a real connectome to a virtual connectome of a different type (a *virtual dual*, swapping SC with FC). The second dualization would then map it to a *bivirtual dual* of the same type (mapping SC to SC and FC to FC; cf. Figure 5A).

A first reason to evaluate bi-virtual duals is to perform a self-consistency check of the data completion procedures. If the completion quality is good, then empirical connectomes and their bi-virtual duals should be highly related between them. A second reason would be to generate for each subject a fully virtual pair of connectomes, e.g. a SC_{virt} (or an FC_{virt}) paired with an FC_{bivirt} (or a SC_{bivirt}) that could be shared in a public dataset to avoid disclosing the actual private subject-specific empirical data FC_{emp} (or SC_{emp}).

Figure S5 shows the correspondence between empirical and bi-virtual SC and FC pairs, both when using viable nonlinear (MFM-based) completion procedures and, for completeness, nonviable linear (SLM-based) procedures. We first evaluated the quality of SC_{bivirt} generation over the ADNI-subset of 88 subjects for which a SC_{emp} matrix was available (Figure S5A). Considering the nonlinear bi-virtual completion chain SC_{emp} to FC_{SLM} to $SC_{bi\text{-}SLM}$ we obtained a median correlation between SC_{emp} and $SC_{bi\text{-}MFM}$ of ~0.58. We then evaluated the quality of FC_{bivirt} generation over the ADNI-subset of 168 subjects for which an FC_{emp} matrix was available (Figure S5B). Considering the non-linear bi-virtual completion chain FC_{emp} to SC_{MFM} to $FC_{bi\text{-}MFM}$ the median correlation between FC_{emp} and $FC_{bi\text{-}MFM}$ was also as high as ~0.59.

In the case of SLM-based duals, along the linear bi-virtual completion chain SC_{emp} to FC_{SLM} to $SC_{bi\text{-}SLM}$ we obtained a slightly –but not significantly– better median correlation around ~0.63. However, in the FC_{emp} to SC_{SLM} to $FC_{bi\text{-}SLM}$ direction, the median correlation dropped to ~0.12.

The empirical-to-bi-virtual correlations were always significant and –in all cases but for $FC_{bi\text{-}SLM}$– well compatible with the empirically observed test-retest variability (Wang et al., 2012; Chen et al., 2015; Termenon et al., 2016). This non-trivial performance and, particularly, the fact that empirical-to-bi-virtual correlations in Figure S5 are even higher than empirical-to-virtual correlations in Figures 3, 4 or S1, establish the self-consistency of the model-based data completion procedures presented in Tables 1-2 and S1-S2. Eventually, the degree of bidirectional self-consistency between real and bivirtual duals was higher for non-linear than for linear methods (which constitutes a further argument in favor of the use of more complex nonlinear completion procedures). For nonlinear methods

we also showed that inter-subject relations. Note also that the lack of perfect identity between original seed empirical connectomes and their bi-virtual duals prevents the exact regeneration of the actual subject empirical data (see *Discussion* for the positive implications of this negative result).

Finally, we checked whether bivirtual dualization altered the inter-relations occurring between subjects. In particular, we computed the distances between the empirical connectomes SC_{emp} (or FC_{emp}) of different subjects and the inter-subject distances for corresponding pairs of subjects but, this time, between their bivirtual dual connectomes $SC_{bi\text{-}MFM}$ (or $FC_{bi\text{-}MFM}$). As shown in Figures S5C and S5D, the correlation between the inter-subject distances in real and dual spaces were noticeable and significant, reaching CC=~0.34 between SC_{emp} and $SC_{bi\text{-}MFM}$ (Figure S5C; bootstrap 95% c.i. $0.31 \leq CC \leq 0.36$) and CC=~0.46 between FC_{emp} and $FC_{bi\text{-}MFM}$ (Figure S5D; bootstrap 95% c.i. $0.45 \leq CC \leq 0.47$). We also noticed that distances between bivirtual duals were often amplified, with respect to the original empirical distances. The space of dual bivirtual connectomes can thus be considered as a "virtual mirror" of the real connectome space, reproducing to a reasonable extent despite some deformation of the geometry of the original distribution of subjects.

Subject classification based on real and virtual connectomes

The compilation of large datasets, including connectivity data from structural and functional neuroimaging is considered essential for the development of algorithmic patient stratification and predictive approaches. Here, we have described approaches for connectomic data completion and studied their consistency. We now show that such completion procedures are also compliant with the extraction of information via machine learning algorithms.

As a proof-of-concept, we studied a simple classification problem, the one of separating the ADNI subjects into two subgroups, constituted respectively of *control* subjects and *patients* (MCI or AD). We used target classification labels already provided within the ADNI dataset, assuming them to be exact (see *Materials and Methods* for a summary of the used stratification criteria). We performed classification based uniquely of network properties of some the following connectome matrices (for the subject subsets for which they are available): empirical SC_{emp} or FC_{emp}; their virtual duals FC_{MFM} or SC_{MFM}; or their bivirtual duals $SC_{bi\text{-}MFM}$ or $FC_{bi\text{-}MFM}$ (see Figure 5A). In Figure 5B and 5C, we focus in particular on predictions based on the regional *node strengths* estimated subject-by-subject from the connectome matrices of interest (Q = 96 input features, corresponding to the number of brain regions in the used parcellation, see *Materials and* Methods). As supervised classifier algorithm, we chose then a variant (Seiffert et al., 2010) of the random forest algorithm, which is particularly suitable when the number of input features is of the same order of the number of available data-points in the training set (Breiman, 2001), as in our case.

We considered first classification based on real connectomes, based on SC_{emp} matrices (green line, Figure 5B) or on FC_{emp} matrices (green line, Figure 5C). The available subjects were randomly split into a training set and a testing set (with maintained relative proportions of the different classification labels). We show in Figures 5B and 5C the average generalization performance for classifiers trained on the training set and evaluated on a testing set. Training and testing on real empirical connectomes, we achieved a moderate but significantly above chance level classification performance, as revealed by the green Receiver-Operator-Curves (ROC) in Figures 5B and 5C, for both SC_{emp} and FC_{emp} connectomes, deviating away from the diagonal (corresponding to chance level classification performance).

We considered then classification based on virtual and bivirtual duals instead of empirical connectomes. In this case of "dual space classification" (Figure 5B), virtual and bivirtual duals are used both when training the classifiers and when evaluating them. Therefore, to classify a new empirical connectome with a "dual space classifier", it is first necessary to "lift" it in dual space, i.e. to map it via data completion algorithms to the suitable type of dual for which the classifier has been trained. Figure 5B shows an example of dual space classification based on FC_{MFM} and SC_{biMFM} (Figure 5B, magenta curve), respectively virtual dual and bivirtual duals of the real connectomes SC_{emp}. Once again, Figure 5B shows average ROC curves for classification based on duals (Figure 5B, blue curve for virtual duals FC_{MFM}; magenta curve for bivirtual duals SC_{MFM}). For both virtual and bivirtual duals, classification performance remained robustly above chance level. While the classification performance tended to drop slightly with respect to classification with the actual empirical connectomes, this drop was not significant for a broad range of the most conservative decision thresholds, leading to small false positive fractions. Classification is thus possible as well using dual connectomes generated from data completion, achieving performances substantially equivalent to the one obtained for empirical connectomes.

We considered finally the case of classifiers trained on bivirtual duals and then evaluated on empirical connectomes (Figure 5C). In this case of "cross-space classification", the trained classifier is able to operate in a performing manner as well on a different type of connectomes (e.g. empirical) than the one for which it has been trained (e.g. bivirtual dual). Therefore, to classify a new empirical connectome with a "cross-space classifier", it

is not necessary to first lift in dual space as for dual space classifiers. Figure 5C shows an example of cross-space classification trained on bivirtual dual FC_{biMFM} and then tested on FC_{emp} (Figure 5C, orange curve). Remarkably, the performance was barely distinguishable and not significantly different for most decision thresholds from classification trained and tested on empirical FC_{emp} connectomes. Therefore, classification of empirical connectomes based on classifier trained on virtual connectomes is possible as well.

Similar results can be obtained for other examples of dual space and cross-space classifications. The Area Under Curve (AUC) performance measure –similar for different classifier combinations and thus here pooled together– were: in the 95% confidence interval range $0.52 \leq AUC_{median} = 0.67 \leq 0.80$ for direct classification (trained and tested on empirical connectomes); and in the overlapping range $0.51 \leq AUC_{median} = 0.60 \leq 0.72$, for all classifiers involving virtual or bivirtual duals confounded (dual space or cross-space classifications). In general, even when classification significantly above chance level could be obtained, the achieved performance was never extraordinary. The aim was not here nevertheless to raise performance –the chosen classification problem itself being rather irrelevant– as much as to show that empirical and virtual duals convey similar amounts of information in an illustrative application. This informational equivalence can be shown even better by revealing the similarity of network topology features between real connectomes and their bivirtual duals, independently from our capacity to achieve more or less performing classifications based on these features.

Matching network topology between real and virtual connectomes

The connectome matrices describe the weighted undirected topology of graphs of structural or functional connectivity. All information conveyed by these connectomes about pathology or other conditions is potentially encoded into this network topology. While genuine model-free analyses of network topology across all scales are still under development –see for instance, promising topological data analyses approaches (Petri et al., 2014; Sizemore et al., 2018)–, classic graph theoretical features provide a first multi-faceted characterization of the specific features of each individual connectome object (Bullmore & Sporns, 2009). We evaluated here for each empirical connectome SC_{emp} or FC_{emp} a spectrum of different graph theoretical features. In particular we evaluated for each brain region within each of the connectomes (see *Materials and Methods* for details): the total *strength* (sum of the connection weights of all the links incident the region); the *clustering coefficient* (tendency of the regions neighboring to the considered node to also be interconnected between them); and *the centrality coefficient* (tendency for any path linking two different nodes in the network to pass through the considered node), evaluated via the PageRank algorithm (Brin & Page, 1998). We also evaluated for each connectome its *modular partition* into communities, by using a Louvain algorithm with default parameters (Blondel et al., 2008). We then evaluated analogous quantities for the bivirtual dual connectome associated with each of the connectomes.

In Figure 6 we illustrate the correspondence between graph-theoretical features evaluated for different real/bivirtual dual connectome pairs. To compare node degrees, clustering and centrality features we plot, for every brain region in every connectome, the feature value evaluated in a real connectome against the corresponding feature value evaluated in the associated bivirtual dual. To compare community structures, we evaluate for every real/bivirtual dual connectome pair the relative mutual information MI normalized by entropy H (see *Materials and* Methods) between the community labels extracted for the two connectomes, with $0\% \leq MI/H \leq 100\%$ and 100% corresponding to perfect overlap. We show results for SC real/bivirtual dual pairs in Figure 6A and for FC pairs in Figure 6B. In all cases we find correspondence between real and bivirtual dual connectome features significantly above chance levels. Highly significant real/bivirtual dual correlations subsist for regional strengths and centralities. For FC, these correlations can become as high as $0.52 \leq CC_{median} = 0.64 \leq 0.71$ (95% bootstrap confidence interval) for regional strengths and $0.37 \leq CC_{median} = 0.52 \leq 0.65$ (95% bootstrap confidence interval) for regional centralities. Correlations are found even for regional clustering coefficients, even if the small values of clustering coefficients observed in SC_{emp} connectomes are systematically overestimated in the denser bivirtual dual SC_{biMFM}. Finally, concerning community matching, for both SC and FC real/bivirtual dual pairs we found a median relative mutual information of ~58%, safely above chance level (estimated at ~16%, permutation-based 95% confidence interval).

The analyses of Figure 6 are performed at the ensemble level, i.e. pooling network features estimated from different subjects into a same point cloud. However, network features can have important variations of values not only across regions but also across subjects. Therefore, we computed correlations between regional features in real and empirical connectomes even *within* individual subjects (compiled in Table 3), obtaining thus for every feature type, a different correlation value for every subject. Table 1 shows that within-subject correlations were also high (apart for SC clustering) and, for FC, even superior to ensemble-level correlations. Importantly, these correlations were robustly *personalized*. Indeed, when computing personalized correlations for pairs of connectomes which were actually dual –i.e., real and bivirtual connectomes associated to a same matching subject– they resulted systematically superior to unpersonalized control correlations evaluated over real/bivirtual connectome pairs assembled out of different subjects (see *Materials and Methods*). Percent improvements in same-subject real/dual correlations with respect to average correlations in cross-subject pairs are compiled as well

in Table 3. Personalization can lead to very strong percent improvements in real/virtual topology correlations, particularly in the case of FC connectomes. The operation of dualization thus preserves aspects of network topology which are specific to each subject and not just generic to a connectome ensemble. In conclusion, data completion procedures lead to a refined correspondence of the network topology details between real and bivirtual dual pairs, which is a necessary condition for personalized predictive information preservation.

Virtual cohorts

All nonlinear data completion algorithms involve a stochastic component. Therefore, by construction, each simulation run will provide different virtual and bi-virtual connectomes, associated with the same empirical seed connectome. This property allows the generation of an arbitrarily large ensemble of surrogate virtual connectomes, forming the *virtual cohorts* associated with a specific subject (see *Materials and Methods*). Every virtual cohort maintains a strict relation to its empirical counterparts because all the matrices in the cohort are dual to the same original empirical connectome. In particular, distances between virtual connectomes sampled within two different virtual cohorts were always closely correlated to the distance between the respective seed connectomes of the two cohorts. The close relationship between the original data and the respective virtual cohorts (already studied in Figure S5C and S5D for individual instances of bivirtual connectomes) is visually manifested in Figure 5D, where a distance-respecting non-linear t-SNE projection (Van Der Maaten & Hinton, 2008) has been used to represent in two dimensions the virtual cohorts of surrogate virtual FC_{MFM}'s associated to the 88 subjects with available SC_{emp}. Every dot corresponds here to the two-dimensional projection of a high-dimensional virtual dual FC_{MFM} (100 different virtual FC_{MFM}'s have been generated starting from each one of the 88 SC_{emp} connectomes). Clusters of dots are visually evident in the projection indicating that the distance between dual connectomes within each virtual cohort is smaller than the distance between dual connectomes belonging to different cohorts. The connectomes composing the virtual cohorts represented in Figure 5D can be downloaded as Supporting File S5.

Therefore, learning performed on virtual cohorts is expected to generate similar discrimination surfaces as learning on the original subjects, with the added benefits that training items in cohorts are way more numerous than the original empirical data, a fact that may become in perspective beneficial to training (see *Discussion*).

Discussion

We have here demonstrated the feasibility of connectomic dataset completion using algorithms based on mean-field computational modeling. In particular, we have completed an ADNI gold standard connectomic dataset. We have then shown that machine learning classifiers trained on virtual connectomes can reach comparable performance to those trained on empirical connectomes. This renders the classification of novel empirical connectomes via classifiers trained exclusively on virtual connectomes possible. Furthermore, the generation of virtual and bivirtual dual connectomes is a procedure preserving precious personalized information about detailed network topology. As a consequence, virtual cohorts offer an immense opportunity to improve, and sometimes to enable or unblock, machine learning efforts on large patient databases.

Incomplete datasets for clinical research are certainly among the factors contributing to slow progress in the development of new diagnostic and therapeutic tools in neurodegenerative diseases and Alzheimer's disease (AD) in particular. Our data completion procedures provide a step forward toward "filling dataset gaps" since they allowed us to infer Functional Connectivity when only Structural Connectivity was available or Structural Connectivity (SC) when only Functional Connectivity (FC) were available. Such procedures for data completion could easily be implemented within popular neuroinformatic platforms as The Virtual Brain (TVB). TVB provides practical graphical interfaces or fully scriptable code-line environments for "plug-and-play" large-scale brain network behavior, signal emulation, and dataset management, including simulating SC and FC with adjustable complexity MFMs or SLMs (Sanz-Leon et al., 2013). In this way, capitalizing on the software built-in capabilities, even the more elaborated non-linear completion algorithms could become accessible to non-expert users with only a little training. The possibility of having access to both types of connectomic information brought up by model-based data completion is vital because structural and functional connectivity convey complementary information. It has been shown for instance, that analyses of SC-to-FC inter-relations can yield better characterizations and group discriminations than analyses of SC or FC alone in a variety of pathologies or conditions (Zhang et al., 2011; Davis et al., 2012; Zimmermann et al., 2016; Straathof et al., 2019).

Indeed, FC networks in the resting-state do not merely mirror SC but are believed to be the by-product of complex dynamics of multi-scale brain circuits (Honey et al., 2007; Deco et al., 2011). As such, they are constrained but not entirely determined by the underlying anatomy (encoded in the SC matrix) and FC also carries

valuable information about the dynamic regime giving rise to the observed resting-state activity fluctuations (Hansen et al., 2015). In particular, brain networks are thought to operate at a regime close to criticality. For a fixed SC, the resulting FC would be different depending on how closely dynamics is tuned to be in proximity of a critical working point (Deco et al., 2013; Hansen et al., 2015). This information that brain networks are supposed to operate close to a critical boundary is used to generate the surrogate virtual FC_{MFM}, when performing non-linear SC-to-FC completion. Thus, FC_{MFM} carries indirectly extra information about a (putative) dynamic regime that was not conveyed by the original empirical SC (nor by virtual completions with linear SLM-based pipelines). This nonlinear reconstruction schemes compensates in part for the loss of information occurring ineluctably along any algorithmic processing chain –according to the "data processing inequality" (Cover & Thomas, 2006)– and may be responsible for the superior performance of nonlinear with respect to linear data completion. It thus may be considered as a form of "reinjection" or "sharpening" of information, present in the full data set. It is not a form of the invention of information.

When both empirical SC and FC were available, we could measure the quality of reconstruction achieved by our models. The correlation reached between empirical and reconstructed connectivity matrices is only moderate, however. There are multiple reasons for this limited performance. One evident reason is the simplicity of the neural mass model adopted in our proof-of-concept illustration. The Wong-Wang neural mass model is able only to express two states of lower or higher local activation (Wong & Wang, 2006). Instead, neuronal populations can display a much more extensive repertoire of possible dynamics, including e.g., coherent oscillations at multiple frequencies, bursting, or chaotic trajectories (Stefanescu & Jirsa, 2008; Spiegler et al., 2011). Synchronization in a network depends on various factors, including frequency, network topology, and time delays via signal propagation, all of which have been ignored here and in large parts of the literature (Deco et al., 2009; Petkoski & Jirsa, 2019). It is acknowledged that delay-less approaches serve as a useful approximation (Deco et al. 2015). Nevertheless, we are aware that our choice to restrict our analyses on the subset of activation-based mechanisms introduces critical limitations. Indeed, our models, ignoring delay-mediated synchronization, are incapable of capturing a range of dynamic oscillatory behaviors, such as multifrequency coupling or multiphase coupling. More sophisticated mean-field virtual brain models than the very simple one here explored could thus reach superior performance (see e.g. Stefanovski et al., 2019).

Yet, even such a simple model, achieving such a limited reconstruction performance proved to be consistent and useful. First, when concatenating data completion pipelines to give rise to bi-virtual data, we found a robust self-consistency, i.e. remarkable matching between e.g. the original SC (or FC) and the bi-virtual $SC_{bi\text{-}MFM}$ (or $FC_{bi\text{-}MFM}$) generated via the intermediated FC_{MFM} (or SC_{MFM}) step. This self-consistent correspondence is not limited to generic correlations but captures actual personalized aspects of detailed network topology (Table 1 and Figure 6). Second, classification performance reached based on empirical data could be equated by classifiers trained on virtual or bivirtual dual connectomes (Figure 5B and 5C). Therefore, even if the reconstruction quality of our model-based completion procedures is modest, a meaningful relationship with the original seed data is still maintained, even after two steps of virtual completion. The use of simple models has the additional advantage of being less computationally expensive to simulate. Note that SLMs would be even simpler and faster to run than our basic MFMs but that their completion performance is insufficient (Figure S2). Therefore, basic MFMs as our virtual brains based on the Wong-Wang model provide a reasonable compromise between computational speed and the need to render structured brain dynamics beyond mere Gaussian fluctuations (Haken, 1983) constrained by SC.

We have provided in Figure 5 the first proof of concept of the possibility to use virtual and bivirtual connectomes for performing subject classification. For the purpose of classification, data completion procedures are seen as veritable computational bridges between alternative "spaces" in which to perform machine learning, linked by duality relations (Figure 5A). We propose in this respect two possible types of strategy. The first one is to abandon the "real space" of actual empirical connectomes and to operate directly in dual spaces (Figure 5B). In these approaches, empirical connectomes would have to be transformed into their virtual or bivirtual dual counterparts as a necessary pre-processing step. In the second type of strategy, classifiers trained in dual spaces are used to operate in the real space. While such approach doesn't require the virtualization of empirical input connectomes prior to their classification, performance could be potentially reduced by a possible systematic mismatch in input feature distributions between real and dual spaces (as seen in Figure 6, for instance, some network features such as SC clustering tend to get overestimated in dual connectomes). The two specific examples highlighted in Figures 5B and 5C show comparable qualities of classification for dual space and cross-space classifications (in both cases, not significantly decreases with respect to classification in real space). In general, we could not find statistically significant differences in the performances of dual space and cross-space classifiers. It is however true that, generally, we were able only to reach poor classification performances, barely above chance level (with an all dual and cross-space classifiers pooled 5% performance quantile of $AUC_{5\%} = 0.51$, as previously said). The performance was not significantly better for direct classification based on empirical connectomes (all direct classifiers pooled 5% performance quantile of $AUC_{5\%} = 0.52$). As a matter of fact, we

have to acknowledge that we are still far from being able to reliably discriminate subject classes based on connectome features, independently from training being performed on real or dual connectomes. We would like to stress that the number of used input features –here $K = 96$, corresponding to the number of regions in the used parcellation (see *Materials and Methods*) for which connectivity strengths were computed– is comparable to the number of subjects in the considered dataset ($N = 88$ or 178 respectively for subjects with available SC_{emp} or FC_{emp}). Therefore, it is not surprising that high performances are difficult to access, even when using classification approaches specially adapted to this situation, as in our case. Superior classification performance could be potentially reached via a more careful feature selection (Guyon & Elisseeff, 2003) that goes beyond the scope of the current study. Nevertheless, our classifiers could reach at least in some training runs performances as high as $AUC_{95\%} = 0.8$ (all direct classifiers pooled 95% performance quantile of AUC, when trained and tested in real space) and $AUC_{95\%} = 0.72$ (all dual and cross-space classifiers pooled 95% performance quantile of AUC, when trained in dual spaces). Hopefully, future attempts to classification will be able to approach more robustly these tendential performances. Given the high degree of personalized correspondence between real and dual connectomes (cf. Table 3), we are confident that any performance level reached by future classifiers trained in real space could be closely approached by classifiers trained in dual virtual and bivirtual spaces.

In perspective, the use of virtual connectomes could become beneficial to the training of machine learning algorithms in a further way. The use of a wider ensemble of surrogate date with statistical distributions of multi-dimensional features equivalent to the original data is a common practice in machine learning, known as *data augmentation* (Yaeger et al., 1997; Taylor & Nitshcke, 2018). Data augmentation is e.g. very popular in object recognition (where surrogate training data are produced by clipping or variously transforming copies of the original training images). Data augmentation aims to expand the training dataset beyond the initially available data to boost the learning by a classifier of the target categories (e.g. object identities). Crucial for dataset augmentation applications is that the surrogate data generated are not just identical to the actual data with some added noise but are genuinely new and can serve as actual good guesses for alternative (unobserved) instances of data-points belonging to the same category. Indeed, if information cannot be created (Cover & Thomas 2006), redundant information can nevertheless improve the performance of decoding and classification (Guyon & Elisseeff, 2003). Computational models such as MFM do not provide mappings between input and output connectomes, but rather between statistical ensembles of connectomes, with both mean and correlated dispersion realistically shaped by trustworthy non-linear dynamics. In other words, differences between alternative connectomes in a generated surrogate virtual cohort are not mere "noise", but reflect realistic data-compliant possibilities of variation. The different connectome realizations sample indeed the specific landscapes of possible FCs that may be compatible with a given SCs, degenerate because the allowed dynamics to unfold along with low-dimensional manifolds, rather than being frozen in strict vicinity of a trivial fixed point (Mehrkanoon et al., 2014; Pillai & Jirsa, 2017). Therefore, given that inter-relations between virtual cohorts mirror inter-relations between empirical subjects (Figure 5D), the generation of surrogate virtual cohorts of arbitrarily large size could provide natural candidates for future data augmentation applications.

Yet, by capitalizing exclusively on redundancy, augmentation cannot replace the gathering of more empirical data (Carrillo et al., 2012; Toga et al., 2016). Unfortunately, federation (or even mining) of data is often impeded by unavoidable juridical concerns linked to strict and diverse regulations (Dulong de Rosnay, 2017; Thorogood et al., 2018) The use of virtual cohorts may once again relieve this burden. Virtual cohorts maintain their statistical relation to the original data, in a way sufficiently good to be exploitable for classification, but do not precisely match the original data, maintaining an inherent variability. This fact may constitute a feature rather than a bug, in the context of data sharing. Indeed, if virtual data carry information operationally equivalent to the one carried by empirical data, they do not carry exactly the same information. It is not, therefore, possible to exactly reconstruct the original subject data from virtualized connectomes, and privacy concerns would be considerably reduced if not entirely removed by sharing dual space images of actual data –eventually demultiplied into virtual cohorts– rather than the original real space data. We thus anticipate a near future in which virtual cohorts, providing vast numbers of virtual and bi-virtual connectivity information, will play an increasing role in massive data-driven explorations of factors predictive of pathology and, in particular, neurodegenerative disease progression.

Materials and Methods

Data Sample

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD).

Raw neuroimaging data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) GO/2 studies (Wyman et al., 2013; Beckett et al., 2015) were downloaded for 244 subjects. These included T1w images for all subjects, as well as DWI and rsfMRI images for separate cohorts of subjects. An additional 12 subjects for which both DWI and rsfMRI were acquired in the same session were identified and their data also downloaded.

A volumetric 96-ROI parcellation was defined on the MNI template and consisted of 82 cortical ROIs from the Regional Map parcellation (Kötter & Wanke, 2005) and an additional 14 subcortical ROIs spanning the thalamus and basal ganglia. Details on the construction of the 96-ROI parcellation can be found in Bezgin et al (2017).

Among the 244 subjects we downloaded, 74 were control subjects, while the others were patients at different stages of the pathology progression. In this study, we performed a rough coarse-graining of the original ADNI labels indicating the stage or type of pathology. We thus overall labeled 119 patients as "MCI" (grouping together the labels 4 patients as "MCI", 64 as "EMCI" and 41 as "LMCI") and 51 patients as "AD" (overall 170 "Patients" for the simple classification experiments of Figure 5).

Overall, T1 and DTI were jointly available for 88 subjects (allowing to reconstruct structural connectivity (SC) matrix), and T1 and fMRI for 178 (allowing to reconstruct functional connectivity (FC)). However, among the 244 subjects we downloaded, only 12 subjects (referred to as the "SC_{emp}+FC_{emp}" subset) had a complete set of structural and functional images (T1, DTI, fMRI), hinting at how urgently needed are data completion and augmentation.

Data Preprocessing

Neuroimaging data preprocessing was done using a custom Nipype pipeline implementation (Gorgolewski et al., 2011). First, raw neuroimaging data were reconstructed into NIFTI format using the dcm2nii software package (https://www.nitrc.org/projects/dcm2nii/). Skull stripping was performed using the Brain Extraction Tool (BET) from the FMRIB Software Library package (FSL v5) for all image modalities prior to all other preprocessing steps. Brain extraction of T1w images using BET was generally suboptimal and was supplemented by optiBET (Lutkenhoff et al., 2014), an iterative routine that improved brain extractions substantially by applying transformations and back-projections between the native brain mask and MNI template space. Segmentation of the T1w images was performed using FSL's FAT tool with bias field correction to obtain into three distinct tissue classes.

To improve the registration of the ROI parcellation to native space, the parcellation was first nonlinearly registered to a publicly-available older adult template (aged 70-74 years, Fillmore et al., 2015) using the Advanced Normalization Tools (ANTS, Avants et al., 2011) software package before subsequent registrations.

Diffusion-weighted images were preprocessed using FSL's *eddy* and *bedpostx* tools. The ROI parcellation was first nonlinearly registered to each subject's T1w structural image and then linearly registered to the DWI image using ANTS.

rsfMRI data were preprocessed using FSL's FEAT toolbox. Preprocessing included motion correction, high-pass filtering, registration, normalization, and spatial smoothing (FWHM: 5 mm). Subjects with excessive motion were excluded from our sample. Global white matter and cerebrospinal fluid signals (but not global mean signal) were linearly regressed from the rsfMRI data.

All images were visually inspected following brain extraction and registrations to ensure correctness.

SC Construction

Details of tractography methods for reconstructing each subject's structural connectome can be found in Shen et al (2019 a, b). Briefly, FSL's *probtrackx2* was used to perform tractography between all ROIs. The set of white matter voxels adjacent to a grey matter ROI was defined as the seed mask for that particular ROI. Grey matter voxels adjacent to each seed mask were used to define an exclusion mask. For intrahemispheric tracking, an additional exclusion mask of the opposite hemisphere was additionally defined. Tractography parameters were set to a curvature threshold of 0.2, 5000 seeds per voxel, a maximum of 2000 steps, and a 0.5 mm step length.

The connection weight between each pair of ROIs was computed as the number of streamlines detected between the ROIs, divided by the total number of streamlines sent from the seed mask. This connectivity information was compiled for every subject in a matrix of empirical structural connectivity SC_{emp}.

rsfMRI Timeseries and FC Construction

Empirical rsfMRI time-series for each ROI were computed using a weighted average approach that favored voxels nearer the center of each ROI (Shen et al., 2012). Each subject's matrix of empirical functional connectivity FC_{emp} was determined by Pearson correlation of these recorded rsfMRI time-series.

SLM models

The SLM model used in this study is a linear stochastic system of coupled Ornstein-Uhlenbeck processes which is deeply investigated in (Saggio et al., 2016). For each brain region, neural activity $x_i(t)$ is modeled as a linear stochastic model, coupled to the fluctuations of other regions:

$$\dot{\boldsymbol{x}}(t) = \boldsymbol{A}\boldsymbol{x}(t) + \sigma\xi(t) \tag{1}$$

where $\boldsymbol{A}$ is the coupling matrix, ξ is a normal Gaussian white noise, and σ the standard deviation of the local drive noise. The coupling matrix $\boldsymbol{A}$ can be written as:

$$\boldsymbol{A} = -\boldsymbol{I} + G.\boldsymbol{W} \tag{2}$$

where $\boldsymbol{I}$ is the identity matrix, G is the global coupling parameter and $\boldsymbol{W}$ is a weight matrix set to match SC_{emp}. The negative identity matrix guarantees that the nodes have a stable equilibrium point. If all the eigenvalues of $\boldsymbol{A}$ are negative, which happens for all positive values of $G < G_{critic} = 1/max(\lambda_i)$ (where λ_i are the eigenvalues of $\boldsymbol{W}$), the system will be in an equilibrium state. After some mathematical steps (Saggio et al., 2016), the covariance matrix between regional fluctuations can be analytically expressed at this critical point G_{critic} as:

$$\boldsymbol{C} = \frac{-\sigma^2}{2}\boldsymbol{A}^{-1} \tag{3}$$

whose normalized entries provide the strength of functional connectivity between different regions. The noise strength can be arbitrarily set at the critical point since it provides only a scaling constant to be reabsorbed into the Pearson correlation normalization. However, the only parameter that needs to be explored is G, whose range goes from $G_{min} = 0$, i.e. uncoupled nodes, to slightly before $G_{critic} = 1/max(\lambda_i)$, or $G_{max} = G_{critic} - \epsilon$. In Figure S1A, running explicit simulations of SLM models for different values of coupling G and evaluating on the "FC_{emp} + SC_{emp}" subset of subjects the match between the simulated and empirical activity correlation matrices, we confirm (cf. e.g. Hansen et al., 2015) that the best match (max of Pearson correlation between the upper-triangular parts of the empirical and virtual FCs) is obtained at a slightly subcritical point for $G^* = G_{critic} - \epsilon$.

Linear SC-to-FC and FC-to-SC completion

Every subject in the "FC_{emp} + SC_{emp}" subset has a different value of G^*. To infer FC_{SLM} from SC_{emp} for the subjects with missing functional data, we chose to always use a common value $G^*_{ref} = 0.83$, which is the median of G^* for all 12 "FC_{emp} + SC_{emp}" subjects (the error made in doing this approximation is estimated to be less than 1% in Fig. S1C). When the connectome FC_{emp} is not known, equations (2) and (3) can directly be used to evaluate the covariance matrix $\boldsymbol{C}$ (setting $\sigma = 1$ and $G = G^*_{ref}$). We then estimate the regional fluctuation covariance from these inferences and normalize it into a Pearson correlation matrix to infer FC_{SLM} (*See pseudo-code in Table S1, line 1*). Linear FC_{SLM} completions for our ADNI dataset can be downloaded as Supporting File S1.

To infer SC_{SLM} from FC_{emp}, we invert the analytical expressions of eqs. (2) and (3) and always set $\sigma = 1$ and $G = G^*_{ref}$ leading to:

$$\boldsymbol{W}^* = -\boldsymbol{C}^{-1}/G^*_{ref} \tag{4}$$

where $\boldsymbol{C}$ is the covariance matrix estimated from empirical BOLD time-series. The linearly completed SC_{SLM} is then set to be identical to $\boldsymbol{W}^*$ setting its diagonal to zero to avoid offsets, which would be meaningless given the conventional choice of noise σ which we have made (*see Table S2, line 3*). Note that all the free parameters of the SLM model appear uniquely as scaling factors and do not affect the (normalized) correlation of the inferred SC_{SLM} with the SC_{emp}. However, the absolute strengths of inferred structural connections remain arbitrary, with only the relative strengths between different connections being reliable (since unaffected by arbitrary choices of scaling parameters; *see pseudo-code in Table S2*). Linear SC_{SLM} completions for our ADNI dataset can be downloaded as Supporting File S3.

MFM models

For non-linear completion algorithms, we performed simulations of whole-brain mean-field models analogous to Deco et al. (2013) or Hansen et al. (2015). We used a modified version of the mean-field model designed by Wong and Wang (2006), to describe the mean neural activity for each brain region, following the reduction performed in (Deco et al., 2013). The resulting neural mass equations are given by:

$$\frac{dS_i}{dt} = \frac{-S_i}{\tau_S} + (1 - S_i)\gamma R_i + \sigma\eta_i(t) \tag{5}$$

$$R_i = \frac{ax_i - b}{1 - exp\,[-d(ax_i - b)]} \tag{6}$$

$$x_i = \omega J_N S_i + J_N G \sum_j C_{ij} S_j + I_0 \tag{7}$$

where S_i represents NMDA synaptic input currents and τ_S the NMDA decay time constant; R_i is collective firing rates; $\gamma = 0.641$ is a kinetic parameter; $a = 270(V.nC)^{-1}$, $b = 108Hz$, $d = 0.154s$ are parameters values for the input-output function; $x_i$are the total synaptic inputs to a regions; $J_N = 0.2609nA$ is an intensity scale for synaptic currents; ω is the relative strength of recurrent connections within the region; C_{ij} are the entries of the SC_{emp} matrix reweighted by global scale of long-range connectivity strength G as a control parameter; σ is the noise amplitude, and η_i is a stochastic Gaussian variable with a zero mean and unit variance. Finally, I_0 represents the external input and sets the level of regional excitability. Different sets of parameters yield different neural network dynamics and, therefore, patterns of FC_{MFM} non-stationarity.

To emulate BOLD fMRI signals, we then transformed the raw model output activity x_i through a standard Balloon-Windkessel hemodynamic model. All details of the hemodynamic model are set according to Friston et al. (2003).

Non-linear SC-to-FC completion

In general, our simple MFM model has three free parameters at the level of the local neural mass dynamics ($\tau, \omega,$ and I_0) and one free global parameter G. Since changing the values of ω and I_0 had lesser effects on the collective dynamics of the system (see Figure S3), we set their values to $\omega = 0.9$ and $I_0 = 0.32$ respectively and remain then just two free parameters which we allow to vary in the ranges $G \in [1\ 3]$ and $\tau \in [1\ 100]$ *ms* when seeking for an optimal working point of the model. As revealed by the analyses of Figure 3, the zone in this restricted parameter space associated with the best FC-rendering performance can be identified through the joint inspection of three scores, varying as a function of both G and τ. The first criterion is the spatial heterogeneity of activation (*see Table 1, line 2.5*) computed by taking the coefficient of variation of $BOLD_{MFM}$ time-series.

By computing the Pearson correlation coefficient of upper-triangular between FC_{MFM} and FC_{emp} for every subject from "SC_{emp} + FC_{emp}" subset (*see Table 1, line 2.3*), we obtained a best-fitting zone in a narrow concave stripe (see Figure 3A for one subject); (G^*, τ^*) parameter set, bring the system to this best-fitting zone and values lower than this is (G^-, τ^-) set and higher values are (G^+, τ^+). This non-monotonic behavior of yellow zone in G/τ plane occurs where three criteria are jointly met; the second criterion is the clustering coefficient of time-average FC_{MFM} matrices (*see Table 1, line 2.6*) and finally, the third criterion is the clustering coefficient of dFC_{MFM} matrices (*see Table 1, line 2.6*), where the dFC matrices were computed for an arbitrary window. By knowing the optimal working point of the system where all three criteria are jointly optimum (*see Table 1, line 2*), we freeze the algorithm and run the non-linear SC-to-FC data completion for 76 subjects (*see Table 1, lines 3 to 5*). Non-linear FC_{MFM} completions for our ADNI dataset can be downloaded as Supporting File S2.

Non-linear FC-to-SC completion

We implemented a heuristic approach to infer the most likely connectivity matrix (i.e. Effective Connectivity) that maximizes the similarity between empirical and simulated functional connectivity. As an initial point, we considered a random symmetric matrix and removed diagonal as $SC^*_{(0)}$ (*see Table 2, line 1*) and run the algorithm in Table 1 in order to simulate the $FC^*_{(0)}$. Then iteratively we adjusted the SC as a function of the difference between the current FC and empirical FC (*see Table 4, line 2*), in other words $SC^*_{(1)} = SC^*_{(0)} + \lambda\Delta FC_{(0)}$ where $\Delta FC_{(0)} = FC_{emp} - FC^*_{(0)}$ and λ is the learning rate (*see Table 4, line 3*). The iteration will stop when the correlation between FC_{emp} and $FC^*_{(k)}$ reaches to the threshold $CC_{target} = 0.7$, and giving the $SC^*_{(k)}$ as SC_{MFM}. All the parameter used in this section is identical to the non-linear SC-to-FC completion procedure. Nonlinear SC_{MFM} completions for our ADNI dataset can be downloaded as Supporting File S4.

Trivial completion using the "other connectome"

For comparison and to assess the non-triviality of data completion performance we also used a trivial "completion" procedure in which the missing connectome (FC for the "SC-only" sub dataset, or SC for the "FC-only" sub dataset) was simply set to be identical to the available connectome (of the "other type"). The performance of such trivial completion approach could be assessed on the "SC_{emp} + FC_{emp}" subset as for any other completion strategy. In order for a completion approach to be considered viable, it is necessary that it outperforms significantly this trivial completion via the "other type" connectome.

Bi-virtual data completion

The pipelines for data completion described above can be concatenated, by performing e.g. FC-to-SC completion on a virtually FC or SC-to-FC completion on a virtual SC (rather than actual FC_{emp} or SC_{emp}, respectively). In this way, one can create bi-virtual counterparts $SC_{bi\text{-}MFM}$ ($FC_{bi\text{-}MFM}$) or $SC_{bi\text{-}SLM}$ ($FC_{bi\text{-}SLM}$) for any of the available empirical SC_{emp} (FC_{emp}) by applying in sequence non-linear MFM-based or linear SLM-based procedures for SC-to-FC and then FC-to-SC completion (or, conversely, FC-to SC followed by SC-to-FC completions). Linear bi-virtual completions for our ADNI dataset can be downloaded as Supporting File S6 (for $SC_{bi\text{-}SLM}$ and $FC_{bi\text{-}SLM}$) and non-linear completions as Supporting File S7 (for $SC_{bi\text{-}MFM}$ and $FC_{bi\text{-}MFM}$).

For every pair of subjects, we computed the correlation distance between the respective empirical connectomes (pairs of FC_{emp} or SC_{emp}) and the corresponding bivirtual duals (pairs of $FC_{bi\text{-}MFM}$ or $SC_{bi\text{-}MFM}$) and plotted the empirical-empirical distances vs the corresponding bivirtual-bivirtual distances (cf. Figures S5C and S5D) to reveal the large degree of metric correspondence between real and bivirtual dual spaces.

Network topology features

To evaluate the correspondence between empirical and bivirtual connectomes we evaluated a variety of graph-theoretical descriptors of the connectomes and compared them within pairs of empirical and bivirtual dual adjacency matrices. Every connectome, functional or structural, was described by a weighted undirected matrix C_{ij}, where i and j are two brain regions, and the matrix entries denote the strength of coupling –anatomical or at the level of activity correlations– between them. For each brain region i, we then computed: its *strength* $S_i = \Sigma_j\ C_{ij}$, indicating how strongly a given region is connected to its local neighborhood; its *clustering coefficient* Clu_i = |triangles involving i| / |pairs of neighbors of i| (with $|\cdot|$ denoting the count of a type of object), determining how densely connected are between them the neighbors of the considered region; and its *centrality coefficient*, quantifying the tendency for paths interconnecting any two nodes in the networks to pass through the considered node. In particular, we computed here centrality using a version of the *PageRank* algorithm (Brin and Page, 1998) for weighted undirected networks in an implementation from the Brain Connectivity Toolbox (Bullmore & Sporns, 2009), with a typical damping parameter of 0.9. Without entering in the details of the algorithm (see Brin and Page, 1998 for details), a node is deemed important according to PageRank centrality if it receives strong links from other important nodes sending selective and parsimonious in their connections, i.e. sending only a few strong links. Strengths, clustering, and centrality measures provide together a rich and detailed portrait of complementary aspects of network topology and on how it varies across brain regions. We computed then the correlations between the above graph theoretical features for matching regions in empirical connectomes and their bivirtual counterparts. In Figure 6 we show point clouds for all subjects pooled together. We then computed correlations even between vectors of graph-theoretical features over the different brain regions within specific

subjects. These within-subject correlations –often higher than global population correlations, since not disturbed by variations of mean feature values across subjects– are summarized in Table 3.

We extracted then the community structure of empirical and bivirtual dual connectomes using the Louvain algorithm (Blondel et al., 2008), with default parameter $\Gamma = 1$ and "negative symmetric" treatment of negative matrix entries (once again, in the implementation of the Brain Connectivity Toolbox). To compare the resulting community assignments to different regions across pairs of dual empirical and bivirtual connectomes we computed the Mutual Information between the respective labelings and normalized it in the unit range by dividing it by the largest among the entropies of the community labelings of each connectome. Such normalised mutual information measure is not sensitive to changes in names of the labels and can be applied independently on the number of retrieved communities. Chance levels for relative mutual information can be estimated by permuting randomly the labels and finding the 99th percentile of values for shuffled labels.

Supervised subject classification

As previously mentioned, we separated subjects in our ADNI-derived dataset in two subgroups: "controls" and "patients" ("MCI" or "AD"). Subjects (the actual ones or their associated virtual counterparts) are thus labeled as "positive" when belonging to the patients subgroup or "negative" otherwise. For illustration, we constructed classifiers based on total strengths (in either SC or FC connectomes, real, virtual, or bivirtual) of different brain regions. The dimension of the input space was thus limited to the number of regions in the used 96-ROIs parcellation, which is of the same order of the number of available subjects in the overall dataset.

We chose as classifier a boosted ensemble of 50 shallow decision trees, training it using the RUSBoost algorithm (Seiffert et al., 2010), particularly adapted to data in which the number of input features is large with respect to the training dataset size and in which "positive" and "negative" labels are unbalanced. For training and testing we split the dataset into 5 folds, each of them with a proportion of positive and negative labels maintained identical to the one of the full dataset and performed training on three of the five folds and testing on the remaining two folds (generalization performance). We considered classifiers in which the training features were of the same type of the testing features (e.g. classifiers trained on SC_{emp} and tested on SC_{emp} data; or classifiers trained on FC_{MFM} and tested on FC_{MFM} data in Figure 5B; etc.). We also considered classifiers in which the type of data differed in training and testing (e.g. classifiers trained on $SC_{bi\text{-}MFM}$ and tested on SC_{emp} data, in Figure 5C). In all cases, generalization performance was assessed on data from different subjects than the ones used for training (i.e. prediction performed on the folds of data not actually used for training). The split in random folds was repeated 1000 times, so to be able to evaluate median performances and their confidence intervals, given by 5th and 95th percentile performances over the 1000 repetitions of training and testing. We measured performance based on the Receiver Operator Curve (ROC) analysis. Notably, we quantified fractions of true and false positives (numbers of true or false positives over the total number of actual positives) during generalization, which depend on an arbitrary threshold to be applied to the classifier ensemble output to decide for positivity of not of the input data. Receiver operator curves (ROC) are generated by smoothly growing this threshold between a minimum (0% of subjects labeled as positive) and a maximum value (100% of subjects labeled as positive) and following how the True (TP) and False positive (TP) fractions vary for the different threshold values (with a diagonal line ROC corresponding to random discrimination). An Area Under the Curve (AUC) was then evaluated as a summary performance indicator, being significantly larger than 50% in the case of performance above chance level). The ROC curves plotted in Figure 5B and 5C, as well as their associated 95% confidence range of variation are smoothed using a cubic smoothing spline based on the cloud of TP and FP values at different thresholds over the 1000 individual training and testing classification runs. We report confidence intervals for AUCs for "direct" classifications (pooling performances for classifiers trained on either SC_{emp} or FC_{emp} and tested on same-type empirical connectomes) and "virtual" classifications (pooling performances for classifiers trained on any type of virtual or bivirtual connectomes and tested on same nature virtual or empirical connectomes) since confidence intervals for more specific types of classifiers were largely overlapping.

Virtual cohorts

To generate virtual cohorts we artificially boosted the size of the original dataset by generating a much larger number of virtual subjects with multiple alternative (but all equally valuable) completions of the missing connectomic data. Concretely, to generate the virtual cohort dataset illustrated in Figure 5D, we took the 88 subjects in the SC_{emp} only dataset (including 21 AD subjects, 35 MCI, and 32 Control subjects) and run for each

of them the non-linear SC-to-FC completion algorithm 100 times, using each time a different random seed. The net result was a group of 100 alternative FC_{MFM} instances for each of the subjects, yielding in total a virtual cohort of 8800 FC_{MFM} matrices to be potentially used for classifier training. Such a cohort can be downloaded as Supporting File S5. To generate Figure 5D, showing a dimensionally reduced representation of the relative distances between these 8800 virtual matrices, we used an exact t-SNE projection (Van Der Maaten and Hinton, 2008) of the vectors of upper-triangular parts of the different FC_{MFM} 's toward a two-dimensional space, using a default perplexity value of 30 and no-exaggeration.

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Tables

Table 1. Pseudo-code for non-linear SC-to-FC completion (FC virtual duals to SC)

```
algorithm non-linear SC-to-FC completion is

external input:  empirical SC (SC_emp)
output: non-linear virtual FC (FC_MFM)
fixed parameters: noise level (σ), simulation time (T), range to scan G_start ≤ G ≤ G_stop, range to scan
     τ_start ≤ τ ≤ τ_stop, other frozen Wong-Wang neural mass parameters

begin
      1.  Construct a MFM embedding SC_emp and the default frozen Wong-Wang neural mass parameters
      for G_start ≤ G ≤ G_stop
         for τ_start ≤ τ ≤ τ_stop
                  2.1 Simulate the MFM with current parameter values for a short time 0.2*T (discarding
                      an initial transient)
                  2.2 Compute surrogate BOLD from MFM time-series via Balloon-Windkessel model
                  2.3 Compute Corr(BOLD), i.e. the time-averaged FC matrix
                  2.4 Compute stream of time-resolved FC(t) and the associated dFC matrix
                  2.5 Compute and store Crit_1[G, τ] (Spatial heterogeneity of activations)
                  2.6 Compute and store Crit_2[G, τ] (Clustering Coefficient of time-averaged FC matrix)
                  2.7 Compute and store Crit_3[G, τ] (Clustering Coefficient of dFC matrix)
         end
      end
      3.  Identify G* and τ* for which Crit_1[G, τ], Crit_2[G, τ] and Crit_3[G, τ] are jointly optimum
      4.  Simulate the MFM with parameter values G* and τ* for a time T (discarding an initial transient)
      5.  Compute surrogate BOLD from MFM time-series via Balloon-Windkessel model
      6.  Compute C = Corr(BOLD), i.e. the time-averaged FC matrix at G* and τ*
      return FC_MFM = C
end
```

Table 2. Pseudo-code for non-linear FC-to-SC completion (SC virtual duals to FC)

```
algorithm non-linear FC-to-SC completion is

external input:  empirical FC (FC_emp)
output: non-linear virtual SC (SC_MFM)
fixed parameters: FC* fitting quality (CC_target), initial guess SC*_(0), learning rate λ, noise level (σ),
     simulation time (T), range to scan G_start ≤ G ≤ G_stop, range to scan τ_start ≤ τ ≤ τ_stop, other frozen
     Wong-Wang neural mass parameters

begin
        1.      FC*_(0) = non-linear SC-to-FC completion starting from SC*_(0)
        2.      Dist = corr(FC*_(0), FC_emp)
        3.      iteration = 0
        while (Dist ≤ CC_target)
                iteration = iteration + 1
                SC*_(iteration) = SC*_(iteration - 1) + λ*(FC*_(iteration) - FC*_(iteration))
                FC*_(iteration) = non-linear SC-to-FC completion starting from SC*_(iteration)
                Dist = corr(FC*_(iteration), FC_emp)
        end
        return SC_MFM = SC*_(iteration)
end
```

Table 4. Single-subject correlations between network features in real and bivirtual dual connectomes

	SC		FC	
	Median and range Within subject, *cross-subject*	Δ%	**Median and range** Within subject, *cross-subject*	Δ%
Strength	0.21 [0.02 < CC < 0.54] *0.13 [0.05 < CC < 0.23]*	**+83%***	0.85 [0.32 < CC < 0.91] *0.20 [0.06 < CC < 0.29]*	**+312%***
Clustering	0.09 [0.01 < CC <0.25] *0.02 [0.001 < CC < 0.04]*	-1% (n.s.)	0.73 [0.12 < CC < 0.88] *0.18 [0.03 < CC < 0.29]*	**+304%***
Centrality	0.23 [0.03 < CC < 0.53] *0.15 [0.09 < CC < 0.25]*	**+65%****	0.80 [0.27 < CC < 0.89] *0.17 [0.05 < CC < 0.28]*	**+331%***
Communities	58% [42% < MI/H < 75%] *42% [36% < MI/H < 46%]*	**+43%***	58% [33% MI/H < 80%] *8% [4% < MI/H < 12%]*	**+409%****

*Indicated values for real/bivirtual dual correlations (for strength, clustering and centrality coefficients) or relative mutual information (for communities) are median and 5th and 95th percentiles over subjects. Significance levels for percent improvement due to personalization are given by: *, 5th percentile of improvements positive; **, 1st percentile of improvements positive*

Figures

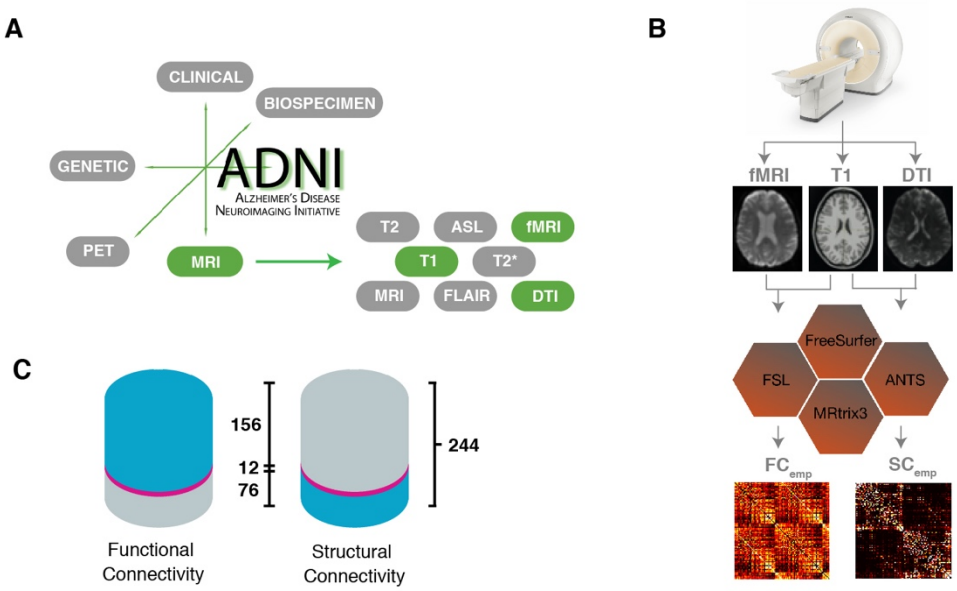

Figure 1. Connectomic information extracted from the ADNI dataset has gaps. A) The different dataset releases by the ADNI consortium include a variety of information relative to different biomarkers and imaging modalities. Here, we focus on structural and functional MRI features and, chiefly: T1, DTI (allowing to extract empirical structural connectomes); and resting-state fMRI BOLD time-series (allowing to extract empirical functional connectomes). B) Matrices SC_{emp} and FC_{emp} summarizing connectomic information about, respectively structural connectivity (SC) and functional connectivity (FC) are obtained via elaborated multi-step processing pipelines, using various software including FreeSurfer, FSL, ANTS, and MRtrix3. C) The total number of ADNI-derived subjects investigated in this study is 244, in which 74 subjects were control, while 119 subjects labeled as MCI, and 51 subjects as AD. Out of these 244, FC_{emp} could be extracted for 168 subjects, and SC_{emp} for 88. However, SC_{emp} and FC_{emp} were both simultaneously available for just a minority of 12 subjects (referred to as the "SC_{emp}+FC_{emp} subset"). The available data is shown in blue and the missing data in grey, the SC_{emp}+FC_{emp} subset is shown in pink.

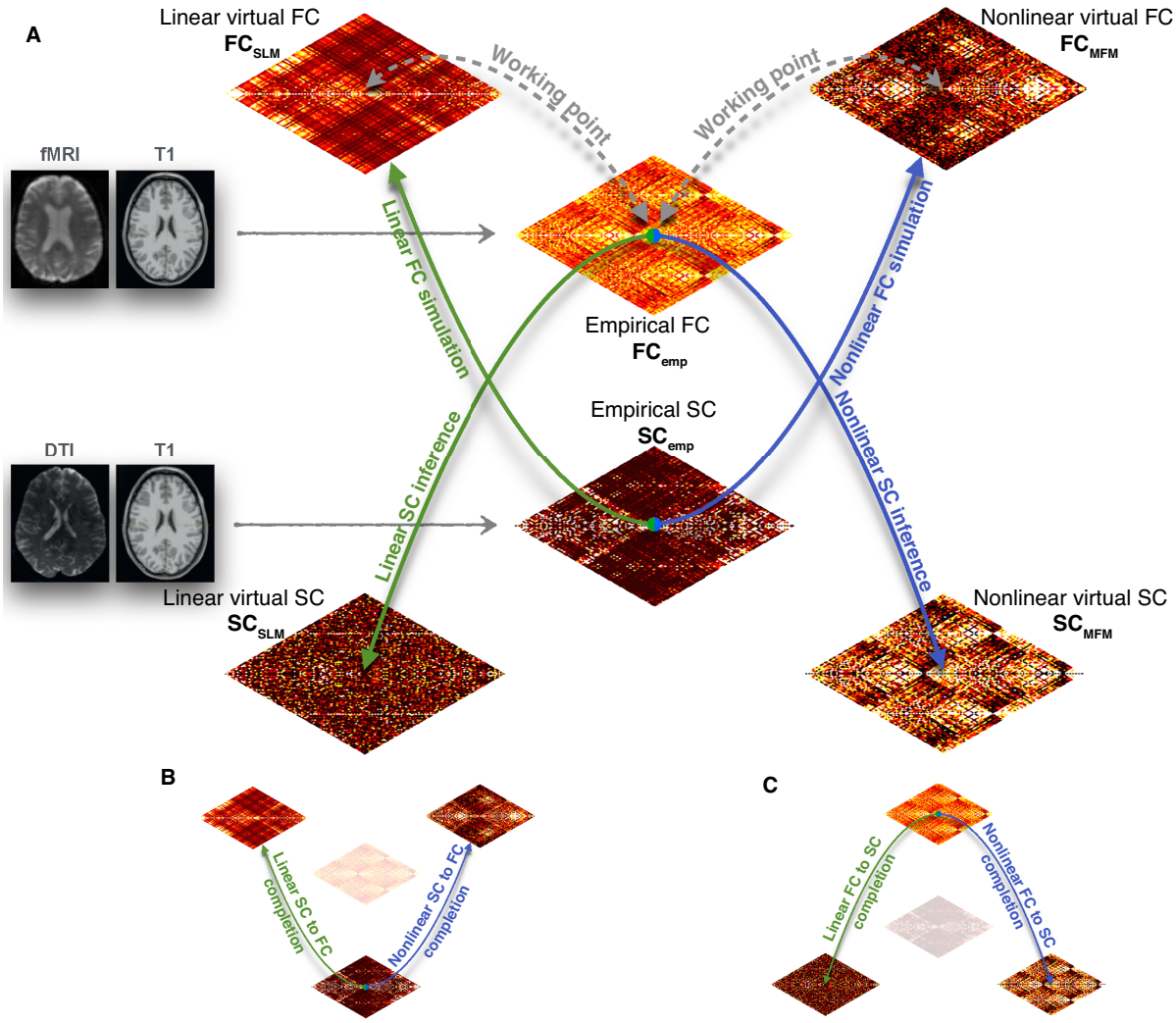

Figure 2. From mean-field modeling to connectomic data completion. A) We present here a graphical summary of the various computational simulation and inference strategies used in this study to bridge between different types of connectivity matrices. Mean-field simulation and the associated analytic theory can be used to generate virtual FC, through simulations of resting-state whole-brain models embedding a given input SC connectome (ascending arrows). Algorithmic procedures, that may still include computational simulation steps, can be used to perform the inverse inference of a virtual SC that is compatible with a given input FC (descending arrows). Both simulation and inference can be performed using simpler linear (green arrows) or non-linear (blue arrows) approaches. When the input SC (or FC) connectomes used as input for FC simulation (or SC inverse inference) correspond to empirical connectomes SC_{emp} (or FC_{emp}), derived from ADNI T1 and DTI (fMRI) images, then model simulation (inversion) can be used to complete gaps in the dataset, whenever FC_{emp} (or SC_{emp}) is missing. We refer then to these operations as: B) SC-to-FC completion; and, C) FC-to-SC completion. Both exist in linear and non-linear versions.

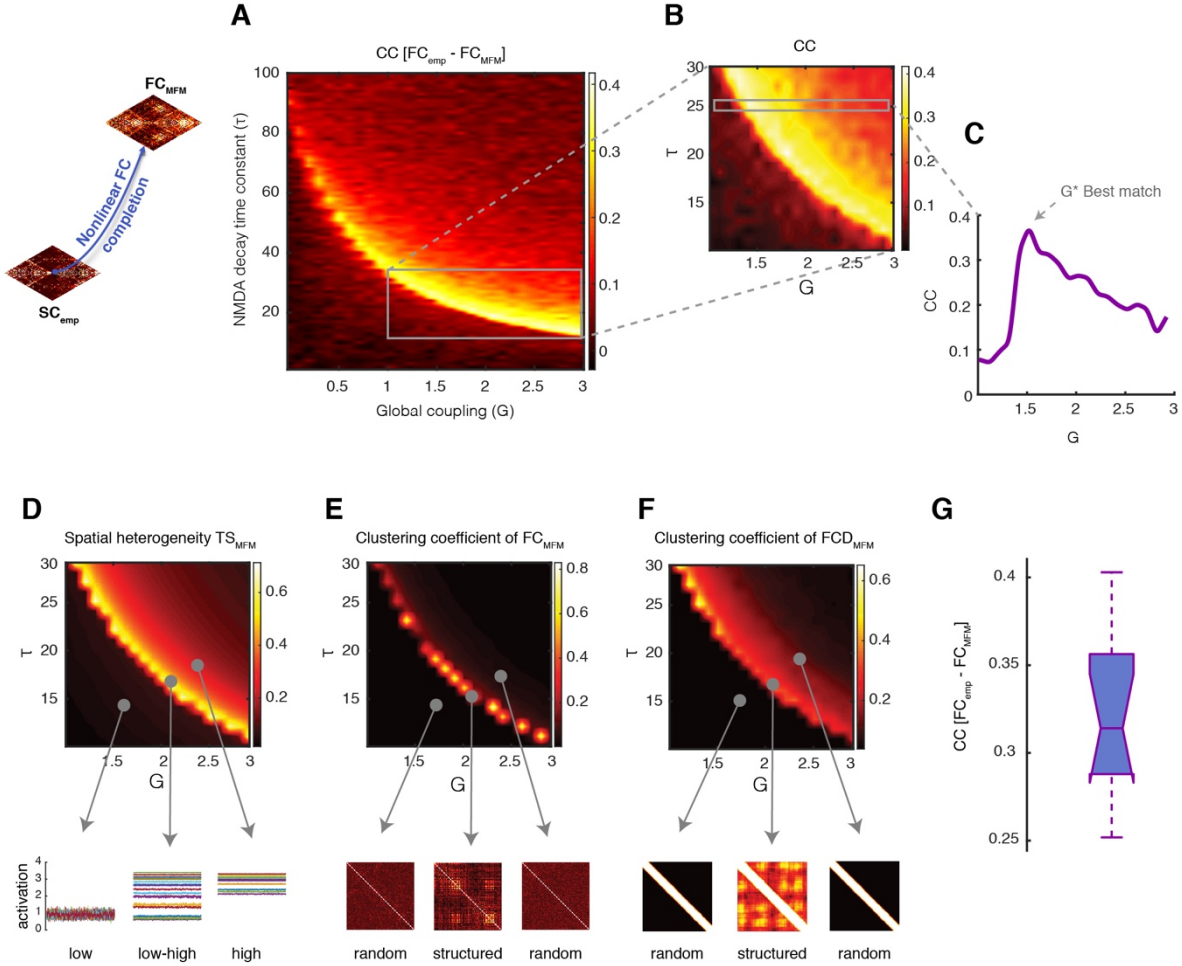

Figure 3. Non-linear SC-to-FC data completion. Simulations of a non-linear model embedding a given input SC_{emp} matrix can be used to generate surrogate FC_{MFM} matrices. A) Systematic exploration (here shown for a representative subject) of the dependency of the correlation between FC_{emp} and FC_{MFM} on the MFM parameters G (inter-regional coupling strength) and τ (synaptic time-constant of within-region excitation) indicates that the best fitting performances are obtained when parameters are concentrated in a narrow concave stripe across the G/τ plane. B) Enlarged zoom of panel A over the range $G \in [1\ 3]$ and $\tau \in [10\ 30]$. C) For a value of $\tau = 25$, representatively chosen here for illustration, we identify a value G^* for which the Pearson correlation between FC_{emp} and FC_{MFM} reaches a clear local maximum. Panels A-C thus indicate that it makes sense speaking of a best-fit zone and that reliable nonlinear SC-to-FC completion should be performed using MFM parameters within this zone. Three criteria help us identifying parameter combinations in this best fitting zone when the actual FC_{emp} is unknown. D) First criterion: we define the spatial coefficient of variation of the time-series of simulated BOLD activity TS_{MFM} as the ratio between the variance and the mean across regions of the time-averaged activation of different regions. The best fit zone is associated with a peaking of this spatial coefficient of variation, associated with a maximally heterogeneous mix or low and high activation levels for different regions (see time-series in lower cartoons). E) Second criterion: in the best fitting zone, the resulting FC_{MFM} is neither randomly organized nor excessively regular (synchronized) but presents a complex clustering structure (see lower cartoons), which can be tracked by a peak in the clustering coefficient of the FC_{MFM}, seen as weighted adjacency matrix. F) Third criterion: in the best fitting zone, resting-state FC_{MFM} display a relatively richer dynamics than in other sectors of the parameter space. This gives rise to an "dFC matrix" (correlation between time-resolved FC observed at different times) which is neither random nor too regular but displays a certain degree of clustering (see lower cartoons). The emergence of complex dynamics of FC can be tracked by an increase in the clustering coefficient of the dFC matrix extracted from simulated resting-state dynamics. G) The boxplot shows the distribution of correlations between the actual FC_{emp} and FC_{MFM} estimated within the best fitting zone for all subjects from the "SC_{emp} + FC_{emp}" subset.

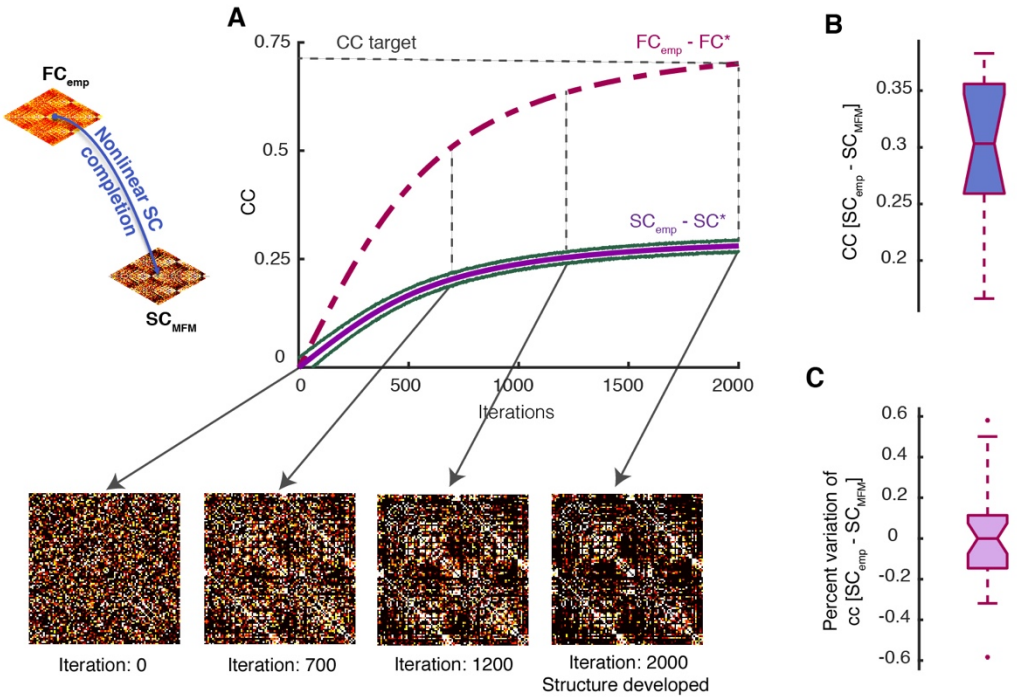

Figure 4. Non-linear FC-to-SC data completion. An iterative procedure can be used to perform resting-state simulations of an MFM model starting from a randomly guessed structural connectome SC* and progressively modify this SC* to make it compatible with a known target FC_{emp}. A) Starting from an initial random $SC^*_{(0)}$ matrix, there is no correlation between the target FC_{emp} and the generated $FC^*_{(0)}$ matrix. However, by adjusting the weights of the used SC* through the algorithm of Table 4, SC* gradually develops a richer organization, leading to an increase of the correlation between FC* and FC_{emp} (violet dashed line) and in parallel, of the correlation between SC* and SC_{emp} (violet solid line), as shown here for a representative subject within the "SC_{emp}+FC_{emp}" subset. The algorithm stops when the correlation between FC* and the input target FC_{emp} reaches a desired quality threshold (here 0.7 after 2000 iterations) and the SC* at the last iteration is used as virtual surrogate SC_{MFM}. B) The boxplot shows the distribution of correlation between SC_{emp} and SC_{MFM} for all subjects in the "SC_{emp} + FC_{emp}" subset. C) The correlation between SC_{emp} and SC_{MFM} can vary using different random initial connectomes $SC^*_{(0)}$. Here we show a boxplot of the percent dispersions of the correlation values obtained for different initial conditions around the median correlation value. The fact that these dispersions lie within a narrow interval of ±2.5% indicates that the expected performance is robust against changes of the initial conditions.

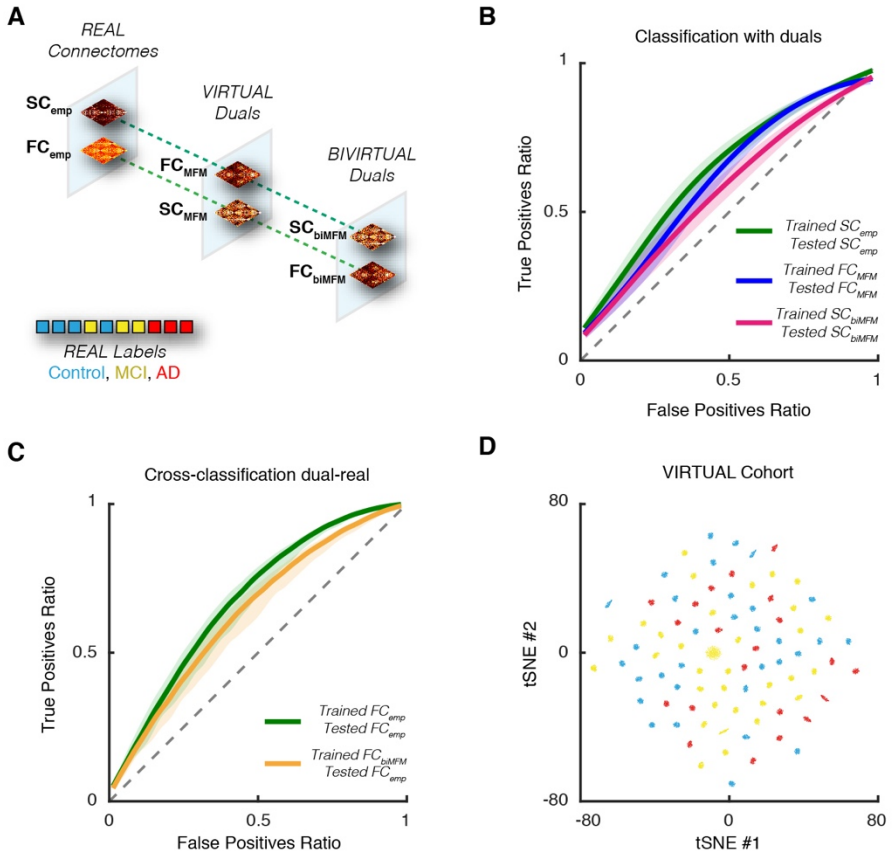

Figure 5. Classification of MCI patients based on empirical and virtual connectomes and virtual cohorts. A) Data completion procedures can be seen as bridges between different connectome spaces, mapping empirical connectomes in "real space" to subject-specific dual connectomes in virtual or bivirtual spaces, depending on the number of virtualization steps applied to the original connectome. Subjects classifications into controls (light blue) or MCI (yellow) and AD (red) patients are shared between empirical connectomes and their virtual and bivirtual duals. Virtual duals have a different nature than their associated empirical connectomes (empirical SCs are mapped to virtual FCs and vice versa), while bivirtual duals have the same nature. B-C) Performance of tree ensemble classifiers discriminating control from patient subjects, evaluated via Receiver Operator Curve analysis (fractions of true vs false positive, as a function of applied decision threshold; generalization performance via crossvalidation; thick lines indicate median performance, shaded regions 95% confidence intervals). In panel B, we show example of classification in dual space, compared with a real connectome space classification: in green classification with classifiers trained on empirical SCs evaluated on other empirical SCs; in blue, classifiers trained on virtual FCs evaluated on other virtual FCs (or the virtual duals of other empirical SCs); in magenta, classifiers trained on bivirtual SCs evaluated on other bivirtual SCs (or the bivirtual duals or other empirical SCs). In panel B, we show an example of cross-space classification, compared with a real connectome space classification: in green classification with classifiers trained on empirical FCs evaluated on other empirical FCs; and in orange, classification with classifiers trained on bivirtual FCs evaluated directly on other empirical FCs, without prior "lifting" into bivirtual dual space. In all the shown cases, classifications performed with classifiers trained in virtual or bivirtual connectomes are slightly less performing than for classifiers trained on empirical data, but the drop in performance is not significant for most thresholds. D) We created virtual cohorts of surrogate FC data, generating 100 different FC_{MFM} matrices for each of the 88 subjects with an available $SC_{emp.}$ Shown here is a low-dimensional t-SNE projection of the resulting 8800 virtual FC_{MFM} 's, colored depending on the associated subject label (same color codes as in panel A). Virtual connectomes within a same virtual cohort are closer between them than connectomes belonging to different cohorts and are thus good candidates for data augmentation applications.

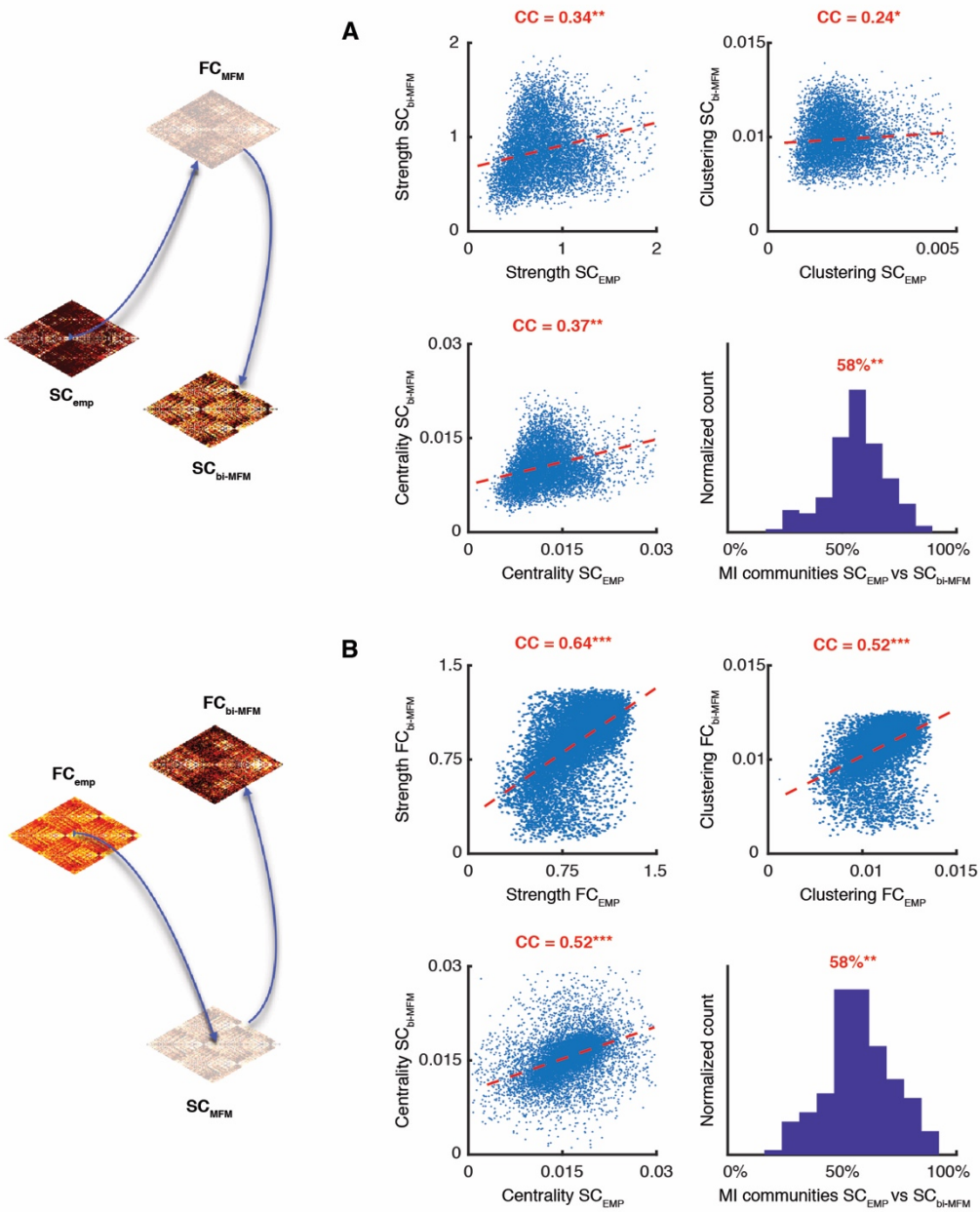

Figure 6. Correspondence of network topology between empirical and their bivirtual dual connectomes. The bivirtual dual connectomes share the same nature (SC or FC) of the corresponding empirical connectome (see Figure 5A). Therefore, network topology can be directly compared between empirical and bivirtual SCs or empirical and bivirtual FCs. A-B) We show here scatter plots of connectivity strengths (top left), local clustering coefficients (top right) and local centrality coefficients (bottom left) for different brain regions and subjects, plotting feature values for empirical connectomes vs their bivirtual counterparts. We also show histograms over different subjects of the relative mutual information (normalized between 0 and 1, the latter corresponding to perfect matching) between the community structures (bottom right) of empirical connectomes and their bivirtual duals. Results are shown in panel A for SC and in panel B for FC connectomes. In both cases, there is a remarkable correlation at the ensemble level between network topology features for empirical bivirtual connectomes (see Table 3 for the even superior correspondence at the single subject level). For scatter plot, stars denote significance of Pearson correlation (bootstrap with replacement confidence intervals: *, $p < 0.05$; **, $p < 0.01$; ****, $p < 0.001$). For histograms: **, median relative mutual information above 99%-th percentile of null hypothesis shuffled distribution (permutation testing).

Supporting Material

Table S1. Pseudo-code for linear SC-to-FC completion

```
algorithm linear SC-to-FC completion is

external input:  empirical SC (SC_emp)
output: linear virtual FC (FC_SLM)
fixed parameters: noise level (σ), guess for optimal G (G*_ref)

begin
      1.  Evaluate the covariance matrix C from SC_emp based on SLM theory for G*_ref
      return FC_SLM = C
end
```

Table S2. Pseudo-code for linear FC-to-SC completion

```
algorithm linear FC-to-SC completion is

external input:  empirical FC (FC_emp)
output: linear virtual SC (SC_SLM)
fixed parameters: noise level (σ), guess for optimal G (G*_ref)

begin
      1.  Evaluate the inverse matrix C^-1 from FC_emp
      2.  Build a matrix S proportional to C^-1 according to SLM theory and drop its diagonal
      return SC_SLM = S
end
```

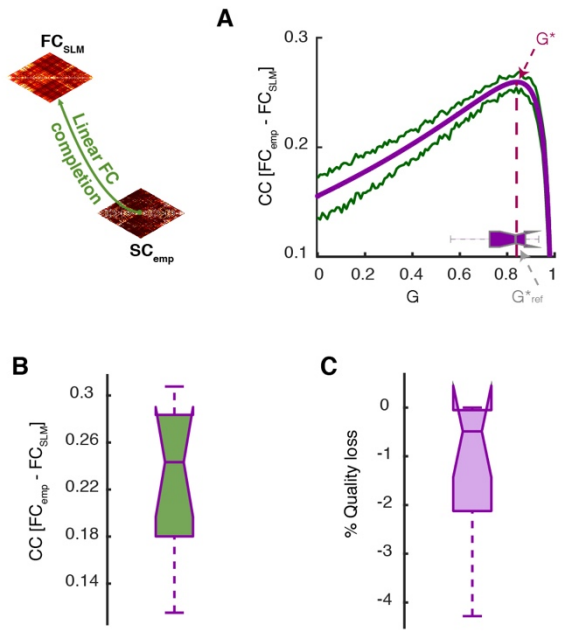

Figure S1. Linear SC-to-FC data completion. The functional data completion can also be done using the linear model starting from SC_{emp} matrices. A) the systematic exploration (for a representative subject) of the dependency of correlation between FC_{emp} and FC_{SLM} on the SLM parameter G (global scale of long-range connectivity strength) shown by the violet line indicates that the best fitting value G^* (dashed line) can be obtained slightly before the critical point of the system $G_{critic} = 1/max(\lambda_i)$ which since the SC_{emp} matrices are normalized to one $1/max(\lambda_i) = 1$ and $G_{critic} = 1$. The green lines display 5 and 95 percentiles of bootstrap resampling. The inset boxplot gives the distribution of G^* over all the subjects in the "SC_{emp} + FC_{emp}" subset; for the SLM SC-to-FC completion, we used a common value $G^*_{ref} = 0.83$, equal to the median of the boxplot. B) The boxplot reports the distribution of Pearson correlation between FC_{emp} and FC_{SLM} for all subjects from the "SC_{emp} + FC_{emp}" subset with a median equal to 0.243. C) In case of using the common value G^*_{ref} for all subjects instead of the actual personalized optimum G^* for each subject in the "SC_{emp} + FC_{emp}" subset, the value of quality loss for each subject is shown in the boxplot with median equal to 0.5%.

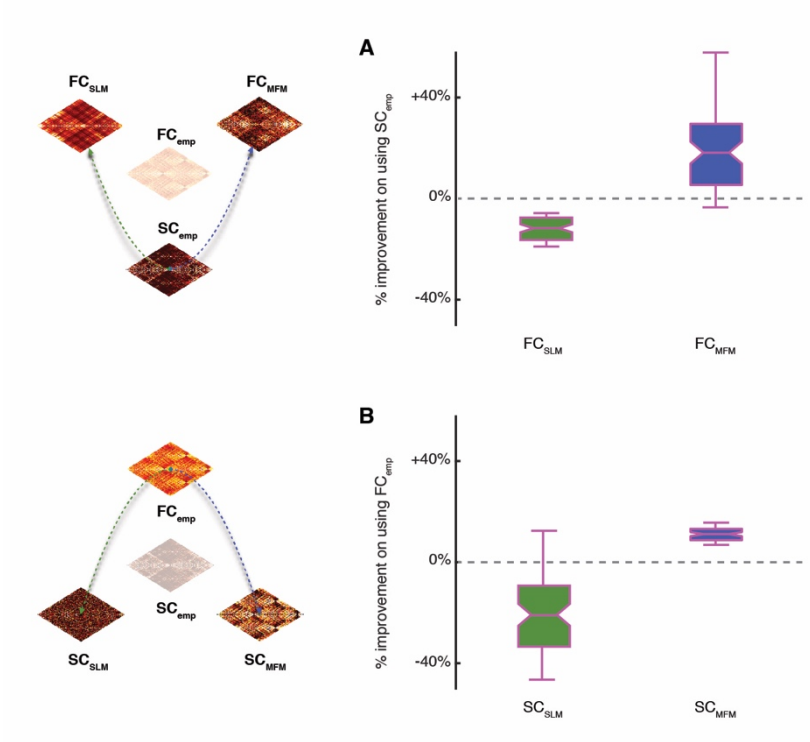

Figure S2. Viability of data completion. We checked whether the performance of data completion based on the algorithmic procedures of Tables 1 and or S1 and S2 is superior to the one of a trivial strategy in which the target connectome to reconstruct is just taken to be identical to the "other connectome" (i.e. using SC, when trying to reconstruct missing FC; or using FC, when trying to reconstruct missing SC). A-B) We computed percent improvement in data completion over the trivial "other connectome" strategy using a SLM-based or an MFM-based data completion method, focusing on the "SC_{emp} + FC_{emp}" subset for which both ground truth connectomes are known. A) Percent improvements in data completion when completing FC from SC. B) Percent improvements in data completion when completing SC from FC. In both directions of completion, MFM-based data completion algorithms bear superior performance with respect to the trivial "other connectome" ersatz. However, SLM-based data completion approaches are not viable, since they do not perform the trivial strategy.

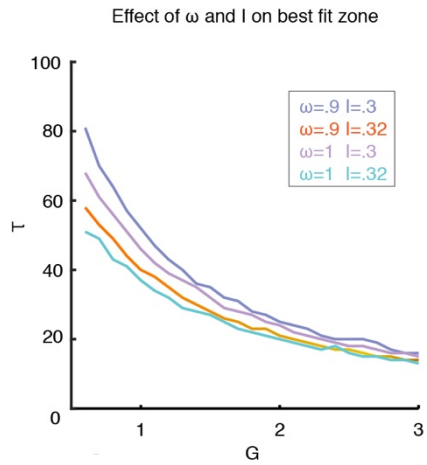

Figure S3. The dependency of best MFM fit zone on additional regional dynamics parameters. In the non-linear data completion, the global parameters of the MFM model are *G* (inter-regional coupling strength), τ (synaptic time-constant of within-region excitation), ω (relative strength of recurrent within-region connections) and *I* (external input) which parameters *G* and τ were investigated in this paper (see Figure 3). Here we showed for different values of ω and *I*, the narrow concave stripe of Figure 3.A as the representative of the best fitting zone is slightly shifted in the G/τ plane, suggesting G and τ are more sensitive parameters and need to be explored rather than ω and *I*.

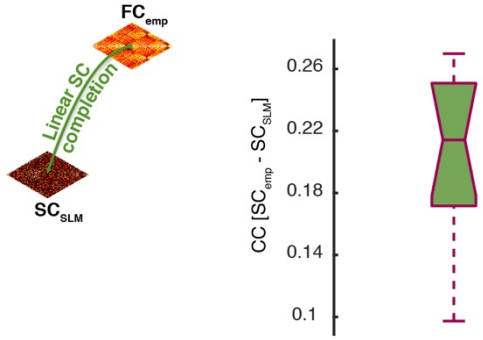

Figure S4. Linear FC-to-SC data completion. Using the linear model, it is equivalently possible to infer the structural SC_{SLM} matrices from FC_{emp}. Since in this approach the free parameters of SLM model appear as scaling factor, they don't affect the correlation of the inferred SC_{SLM} with the SC_{emp} so there is no need for parameter exploration here. The distribution of the correlation values for all the subjects from the "SC_{emp} + FC_{emp}" subset is shown in the boxplot with median equal to 0.21.

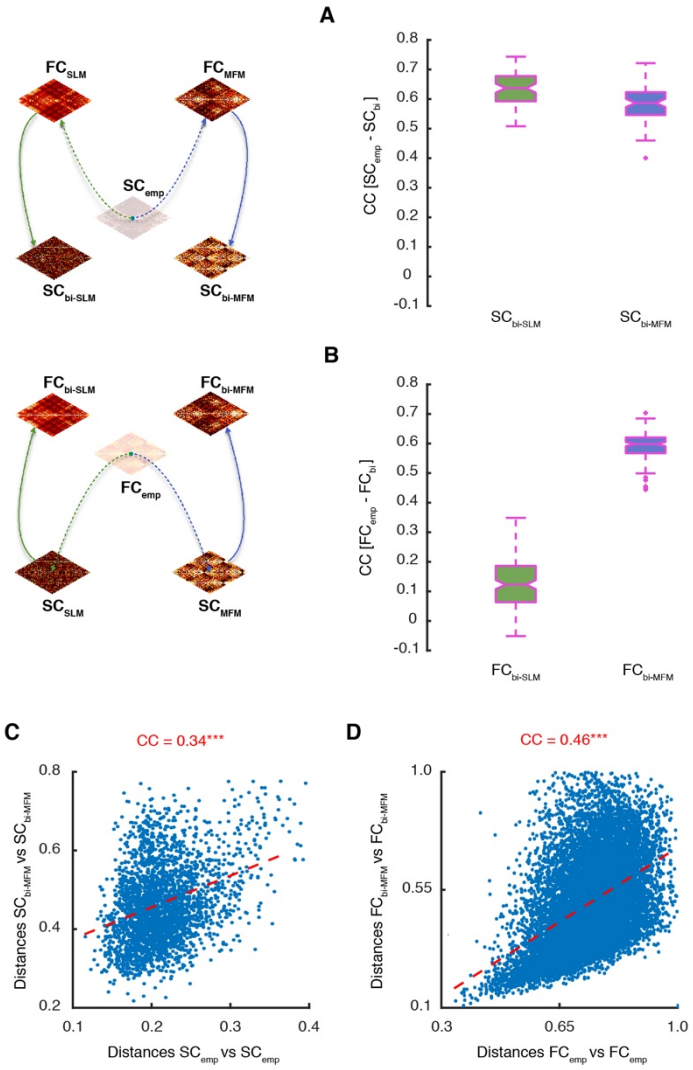

Figure S5. Bi-virtual connectomes. This figure shows the correspondence between empirical and bi-virtual SC and FC pairs, both when using chained linear (SLM-based) and nonlinear (MFM-based) completion procedures. A) For 88 subjects from the ADNI-subset with only SC_{emp} available, considering the linear bi-virtual completion chain SC_{emp} to FC_{SLM} to $SC_{bi\text{-}SLM}$, we obtained a median correlation between SC_{emp} and $SC_{bi\text{-}SLM}$ equal to 0.636 (green boxplot); simultaneously, considering the non-linear bi-virtual completion chain SC_{emp} to FC_{MFM} to $SC_{bi\text{-}MFM}$, we obtained a median correlation between SC_{emp} and $SC_{bi\text{-}MFM}$ equal to 0.583 (blue boxplot). B) For 168 subjects from the ADNI-subset with only FC_{emp} available, considering the linear bi-virtual completion chain FC_{emp} to SC_{SLM} to $FC_{bi\text{-}SLM}$, we obtained a median correlation between FC_{emp} and $FC_{bi\text{-}SLM}$ equal to 0.122 (green boxplot); simultaneously, considering the non-linear bi-virtual completion chain FC_{emp} to SC_{MFM} to $FC_{bi\text{-}MFM}$, we obtained a median correlation between FC_{emp} and $FC_{bi\text{-}MFM}$ equal to 0.597 (blue boxplot). C-D) We show here the distances between the empirical SC_{emp} (or FC_{emp}) of different subjects and the inter-subject distances for their corresponding pairs of subjects from bivirtual $SC_{bi\text{-}MFM}$ (or $FC_{bi\text{-}MFM}$). C) The correlation between the inter-subject distances in real and dual spaces for SC (between SC_{emp} and $SC_{bi\text{-}MFM}$) were significant and equal to 0.34 and D) between FC_{emp} and $FC_{bi\text{-}MFM}$ equal to 0.46.