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PERSPECTIVE

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Clinical Personal Connectomics Using Hybrid PET/MRI

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Abstract
Brain connectivity can now be studied with topological analysis using persistent homology. It overcame the arbitrariness of thresholding to make binary graphs for comparison between disease and normal control groups. Resting-state fMRI can yield personal interregional brain connectivity based on perfusion signal on MRI on individual subject bases and FDG PET produces the topography of glucose metabolism. Assuming metabolism perfusion coupling and disregarding the slight difference of representing time of metabolism (before image acquisition) and representing time of perfusion (during image acquisition), topography of brain metabolism on FDG PET and topologically analyzed brain connectivity on resting-state fMRI might be related to yield personal connectomics of individual subjects and even individual patients. The work of association of FDG PET/resting-state fMRI is yet to be warranted; however, the statistics behind the group comparison of connectivity on FDG PET or resting-state MRI was already developed. Before going further into the connectomics construction using directed weighted brain graphs of FDG PET or resting-state fMRI, I detailed in this review the plausibility of using hybrid PET/MRI to enable the interpretation of personal connectomics which can lead to the clinical use of brain connectivity in the near future.

Keywords Connectivity · PET/MRI · Classification · Persistent homology · Permutation · Connectomics

Several years ago, there was a hope to use hybrid PET/MRI for the evaluation of the neuropsychiatric diseases which could not be characterized for their uniqueness by any brain imaging alone. In most of neuropsychiatric diseases, MRI was normal and FDG PET was normal, too; however, the patients were of course abnormal in their behavior, thought, and affect. These psychopathology should have been associated with characteristic abnormality of brain function and thus the representations on any brain imaging; however, topographical search of abnormality in structure on MRI or in metabolism on PET did not yield consistent or convincing abnormality. As is obviously expected, connection between regions of the brain either in structure or in function represented by T1 signal or FDG uptake was expected to explain the psychopathology of these neuropsychiatric diseases. However, investigators could not know how to discover the unique abnormality of each disease group, which is the classification problem based on brain imaging. For decades now, there had been methodological hurdles hampering the progress in this endeavor, briefly speaking, (1) no established tool to interpret the connectivity of brain regions on individual cases and (2) no way to discriminate the observed connectivity abnormality of a group of disease from that of the normal controls on statistically sound bases. Here, I explain how the investigators overcame these problems recently in order finally to apply the personal connectomics to clinical routines and elaborate further the prospects of desired and long-overdue successful clinical connectomics while emphasizing the remaining problems to be solved. Hybrid PET/MRI is still the best tool to have recourse to by the investigators in this difficult-to-solve joint work which should depend on many disciplines such as topology, mathematics, computer science, statistics, neuroscience, and above all, neuropsychiatry, either basic or clinical.

Interpretation of Topography of MRI and PET for Classification/Prediction

T1 signal and FDG uptake were used to represent the amount of gray matter and glucose metabolism, respectively. To analyze

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T1 signal and FDG uptake quantitatively and statistically, statistical parametric mapping (SPM) were introduced in the early 1990s and evolved to be used to analyze individual differences from the norms on T1 MRI and FDG PET. The method of using SPM to T1 MRI was developed by many researchers and some of them came to be public shareware resource, which is called collectively as voxel-based morphometry (VBM) [1]. VBM of T1 MRI was successfully used to evaluate the longitudinal changes of Alzheimer's disease with the addition of customized introduction of nonlinear registration of the coordinates, and one of which is DARTEL (Diffeomorphic Anatomical RegisTration using Exponentiated Lie algebra) [1]. FDG PET is now being analyzed using SPM with the control of type I error either using random field theory or using false discovery rate (FDR) control on SPM version-up-to-date sharewares (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/), [2].

Though there has been several trials to reduce type II error (false negatives) while controlling type I error (false positives), recent introduction of generalized hierarchical model [3, 4] and inclusion of hidden Markov random field to adjust the adjacency of voxel coordinates enabled to minimize the false non discovery rate (FNDR) successfully [5]. This method includes modeling and estimation and therefore used expectation maximization algorithm and thus slow [5]. Using this method, the previous interpretation of T1 MRI and FDG PET using VBM and SPM, respectively, remains to be re-interpreted, as even the gender differences could be discovered between male and female subjects of normal population [5].

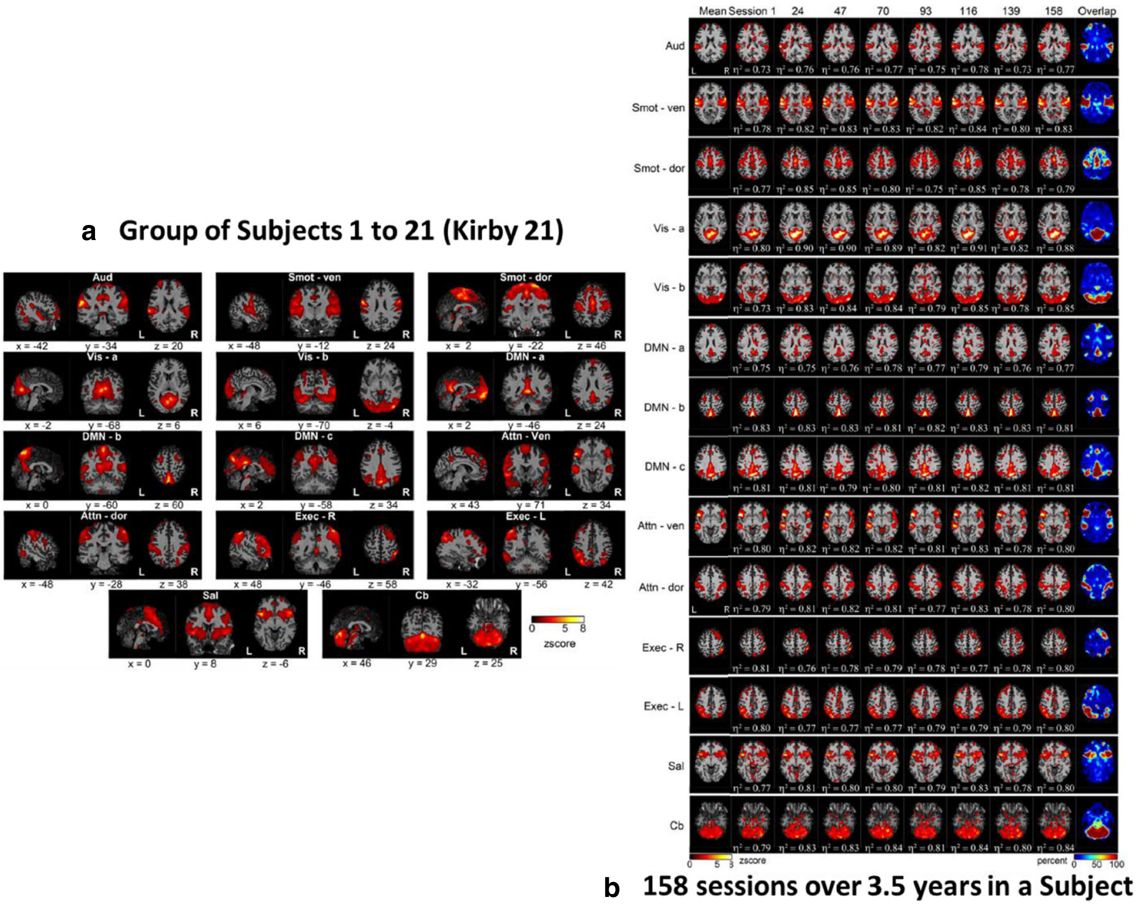
Besides this possible breakthrough, the previous methods to control FDR could not yield convincingly the differences of T1 signal intensity or FDG uptake between patients of a disease group of neuropsychiatric disorders and age-gender-matched control populations. In addition to the classification, investigators have been keen to predict the clinical outcome of the patients with neuropsychiatric disorders in their incipient stages. Discriminating mild cognitive impairment (MCI) converter and non-converter is one of the examples of the problems of this kind. Discovering the inapparent and dormant subjects in the kinship of the patients, or in other words, finding subjects predisposed to a certain disorder is another example to be solved for neuropsychiatric disorders in early ages. In summary, classification and prediction were the two main topics of concern, but topography and its interpretation on T1 MRI and FDG PET have not contributed much as the utility either by visual cognition of the image search and by VBM and SPM analysis and have never been used in clinical routine.

Connectivity and Connectomics on MRI, Functional MRI, and PET

Based on topography, investigators were already interested in the characteristics of connection between brain regions or even voxels. They used task-specific activation fMRI to explain how brain regions are working to orchestrate specific cognitive tasks. For some while, the novel information derived from these investigations prevailed and was considered to be a breakthrough in interpretation of brain topography of blood oxygen level-dependent (BOLD) signals. Functional or effective connectivity was coined to represent this interpretation [6]. The model to explain the connectivity between regions which participated in a certain cognitive task was based on two conditions (basal and task) repeatedly observed on activation fMRI. Of course, the amplitude of BOLD signal on fMRI was used. This was an individual one from a person's fMRI and based on temporally binary observation, i.e., basal and task-related periods. The complicatedness of designing and implementing the activation paradigm with MRI-compatible instruments prohibited further use of this discipline to clinical situations. Instead, resting-state fMRI came to be considered as an alternative to this task-activation fMRI for possible clinical use. However, the resting-state fMRI immediately mandates the assumption that the subjects' brain (or mind) states are stationary during image acquisition of usually 5 min of an epoch (3 s per trial and 100 trials per epoch). The temporal resolutions of 3 s are now lost as they cannot acquire images for interpreting this 3-s periodic transition of mind state to be explored; however again, this 3 s per trial acquisition allows multiple images for easily plausible statistical inference and its production of the regionally coherent amplitude coordination during a certain resting state of subjects undergoing resting-state fMRI study.

Surprisingly, connectivity of resting-state fMRI yielded very robust, stable, and stationary results. In a really persevering study lasting 3.5 years or more published again after 5 years of the completion of the data acquisition, independent component analysis (ICA) interpretation of the summed 158 studies of resting-state fMRI of a subject acquired for 3.5 years every week showed almost the same independent components during the entire study periods [7]. This marvelous authenticity of the resting-state fMRI shows that we now can use this to represent the mind state of a person anytime of the study. Again in the same study, the independent components of this single subject of resting-state BOLD signal were not different from the cohort of 21 subjects. Kirby-21, in NeuroImaging Tools & Resources Collaboratory (NITRC) [7] (Fig. 1). This also means that we now can use resting-state fMRI and its ICA interpretation or independent components thereof to discover the sameness or the discrepancy from those of the normal population.

The term connectomics was proposed by investigators to mean reconstructed microcircuitry of brain derived from a painstaking works of combining fluorescent tomography of brain cells or even electron microscopy of brain slices [8]. Thus, connectomics immediately means each individual's



a Group of Subjects 1 to 21 (Kirby 21)

b 158 sessions over 3.5 years in a Subject

Fig. 1 Consistency of independent components of resting-state fMRI in a population of 21 normal subjects and in a single subject on repeated examination in 158 sessions over 3.5 years (derived with permission exemption with CC from Choe AS et al., PLOS One 2015. Ref [7]). (a) Brain components of single individual were very similar to those of normal controls on independent component analysis using resting-state fMRI. (b) Components were almost the same between 158 sessions in a single individual on independent component analysis

connection pattern. Just like genomics per individuals, or even transcriptomics per states of an individual, connectomics is used to represent an individual's brain connection state and of course connectomes can change over time in terms of connection and connection strength and also of course directed from nodes to nodes, where node means brain region or even voxel. Traditionally, connectivity study presented simply the binary (connected or not) connection patterns cross-sectionally acquired upon time and thus mental states. Now connectomics should be represented on any mental status of performing any tasks or drifting during so-called resting states of mind also on individual bases [7]. Group summation of individuals' brain connectomics can make an assertion that humankind, diseased or normal, will show a specific pattern or norms, respectively.

Statistical inference from repeatedly acquired BOLD signal can give the interregional correlation, which is easily turning into the distance between regions and this distance is making the connection pattern of an individual called connectomics [9, 10]. Instead, T1 MRI or FDG PET can yield individuals' T1 signal intensity or FDG activity of the brain voxels, which only after collecting a group of subjects with the same clinical attributes, such as normal controls or a neuropsychiatric disorder group, could yield multiple topographic image data [11, 12]. Investigators can assume that these multiple image data are derived and sampled from the same group of subjects in the population and thus once errors are handled as noises in the model, they can yield the specific connection pattern of that group. T1 signals or FDG uptakes were successfully used to present connection patterns in various groups of neuropsychiatric disorders [13] or different normal people like the profound deaf [11]. Interregional correlation results were obtained from FDG PET in normal controls, which we put the name of metabolic connectivity [12], using SPM and properly adjusted contrast in generalized linear models. This was the first trial of this kind; however, the completion of this study immediately enlightened the fact that we need a better method and actually better strategic plan to define the problems to be solved and the plausible solution of these problems.

Problems of Connectivity-Connectomics Study and Solving These Problems

Traditionally, connectivity had been presented as graphs which can also be represented with adjacency matrices. Making adjacency matrix using correlation matrix mandates thresholding the distances (square root of (1-correlation)) and though people used sparsity criteria to match the matrices of controls and patients with disorders, there has always been the problem of arbitrariness of determining thresholds [13]. In extreme cases, investigators could make the difference between groups without falsification or fabrication. This raised concerns, which was expressed in various ways including the raising of concern that weak connectivity could be ignored a priori because though there would be no difference between groups at the high threshold, there might be difference between groups at the lenient threshold to make adjacency matrices. Even though investigators tried to use all thresholds to compare groups, there remained the problem regarding which adjacency matrix of one group should be compared with which adjacency matrix of another group [11]. And also, there remains the problem of elucidating statistical difference between groups using all these array of matrices with varying thresholds. We needed to formulate the problem here with totally novel standpoint of looking at the problem.

Firstly, Lee et al. in 2012 [13] adopted the topological analysis method to analyze the graphs and compare the graphs of different groups (Fig. 2). At first, they adopted the filtration of the graphs with varying thresholds, first strict and then gradually lenient, and making single linkage matrix made of single linkage distances between nodes of brain graphs. Here, of course, nodes were the regions of the brain segmented a priori with anatomical information derived from the population mapping reported in the literature and available as shareware. This filtration is based on the mathematical concept of persistent homology for simplicial chain complex and its simplified representation as barcodes for Betti-0, -1, -2, and the higher Betti numbers. To emphasize, this barcode is a shuffled version of dendrogram or single linkage matrix of connected components [14]. The only difference between barcode and dendrogram is the respect for the nodes in the case of dendrogram without shuffling to make barcode (Fig. 3). As single linkage matrix represents connected components and thus is equivalent to minimum spanning tree which can be visualized on 2-dimensional surface. This method was applied to FDG PET [13], T1 MRI [11], activation fMRI [15], MEG [16], and FDG PET in rats [17] and mice [18], too. These were the first systematic application endeavor of topological interpretation of brain graphs.

Secondly, complex graph measures of network science impeded clear understanding of the brain graphs [19, 20]. Based on the framework of persistent homology, these graph measures could be critically reviewed. If brain graphs are made of N nodes, the distribution of degree (p(k); the number of nodes connected to a specific node) can be plotted against the number of degree (k) [21]. If the relationship shows negative linearity on log-log plot between k and p(k), brain graphs are considered to follow hyperbolic geometry. This means that the relationship between nodes will be ruled by hyperbolic geometry. According to the geometric interpretation, degree of nodes is the 0-dimensional characteristics of brain graphs upon nodes and its 1-dimensional equivalent is Ricci curvature assigned to edges and a 2-dimensional one is a sectional curvature assigned to planes [22]. Beyond degree, clustering coefficient or betweenness centrality and other parameters are all related with the node of the graph related with the global graph. Though the whole brain graph determines the nodal characteristics, these parameters are not understood immediately. While nodal global efficiency implies the degree of the nodal fault-tolerance, it means the global graph's capability of compensation of connectivity when the object node is removed [23]. Interestingly, the nodal local efficiency was also proposed to represent the nodal fault-tolerance when the object node is removed from the subgraph consisting of the first neighbors of the object node. Though nodal efficiency has more flexibility than the other parameters and it can represent fault-tolerance of the global graph or the first-neighbor subgraph, all these parameters reflect ambiguous and overlapping and mostly reflecting the nodal characteristics on 0-dimension. They also represent the nodal characteristics of undirected unweighted graphs.

Thirdly, topographical analysis, at its best, though there had been many trials to estimate connectivity, can yield only the pattern of the regional signals, T1 on MRI or FDG uptake on PET [6]. Of course, when the investigators examined functional or effective connectivity, they did not expect that topographical features could replace the connectivity information in general. Though the topographical features resulted from the regional signals connected interregionally within themselves, the solution of finding inter-nodal connectivity from the topographical features has limitation as this is non-deterministic and has one-to-multiple relationship (in other words, ill-posed problem). Convolutional neural networks (CNN) were expected to generate the topology (interregional connectivity) information using just the topography (regional distribution). A convolutional approach on the topographical image data of whatever modality could generate the missing topographical image data of other ages [24] or construct the norms which can be used for determining anomaly of the same modality of imaging [25]. However, the interregional correlation on repeatedly acquired fMRI or population-based T1 MRI or FDG PET yields the information in different (higher) dimensions and cannot be easily estimated with any current deep learning methods. Relational CNN [26–28] and graph CNN [29] might make a breakthrough but we need to wait for their realization.

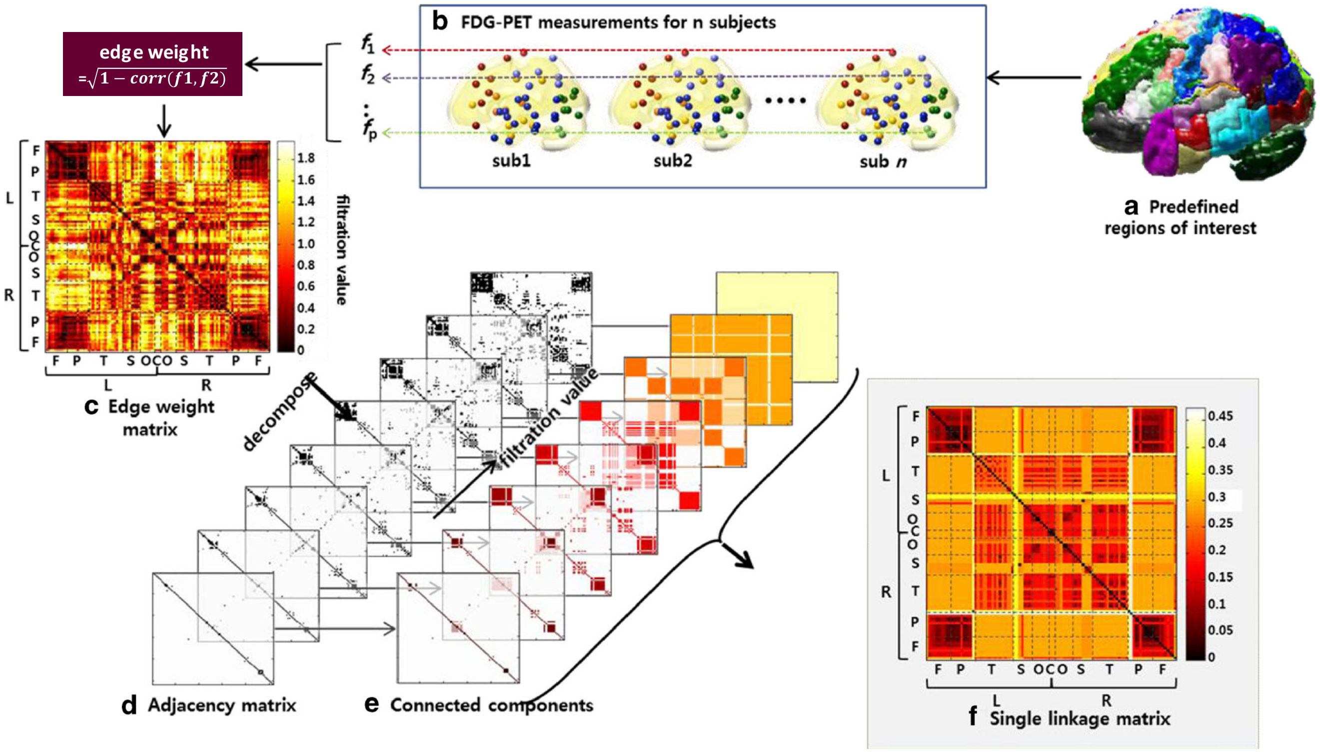


Fig. 2 Scheme explaining the filtration using threshold of edge weight (distance between nodes) to generate single linkage matrix. Predefined regions of interest of the brain yielded FDG uptakes therein (a) to be used to calculate interregional correlation between, for example, f1 and f2 (b). In the case of PET, subjects' variation makes the correlation measureable and edge weights representing the distances between regions are calculated by square root of (1-correlation). Edge weights now make symmetric matrix (c). Using this matrix, by varying the threshold of determining the adjacency to make many binary matrices (d) which in summation will represent the thresholds of edge weight which makes the nodes merge into the components already connected with the previous thresholds (e). Summary matrix is the representation of single linkage distances, in sum, single linkage matrix (f). This single linkage matrix is the Betti-0 or connected components representation on 0-dimension after filtration of simplicial chain complexes based on persistent homology frameworks mathematically (see ref. [14])

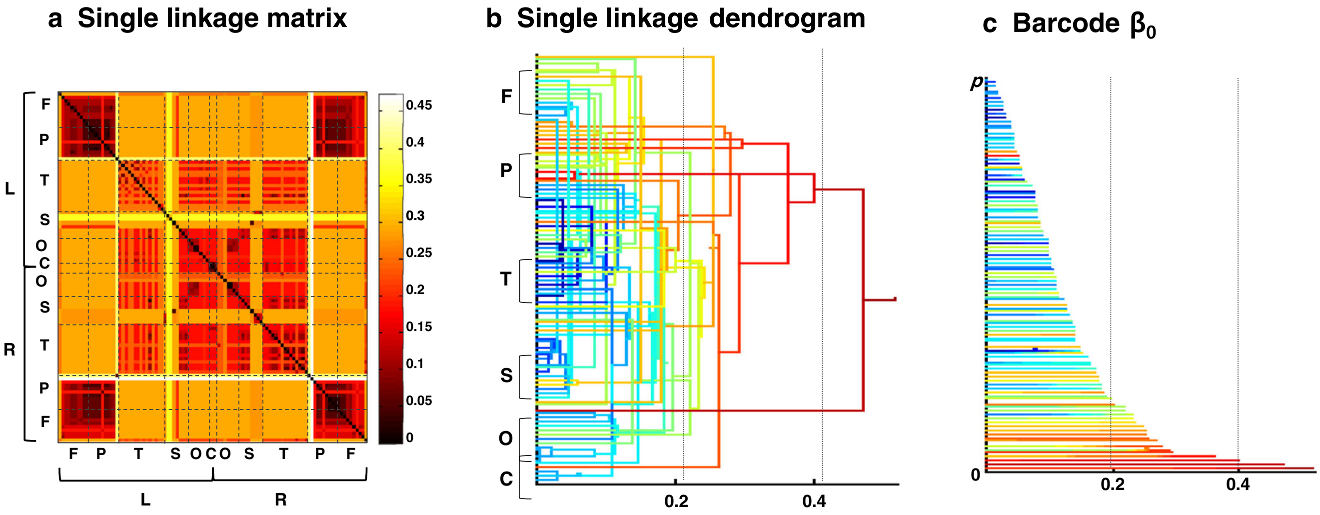
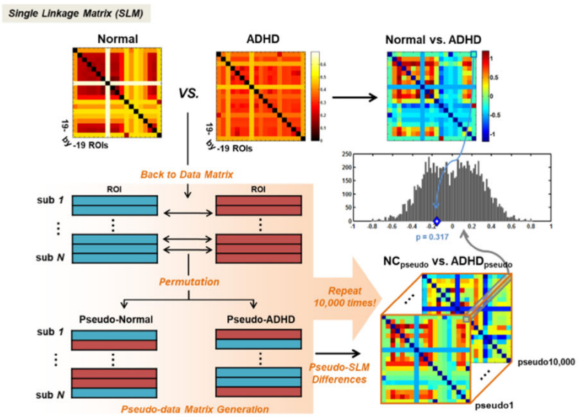


Fig. 3 Equivalence between single linkage matrix and single linkage dendrogram and barcode. (a) Single linkage matrix can be generated by the scheme of filtration detailed in Fig. 2. (b) If we spread brain regions on the *y*-axis and follow their separateness or merging upon filtration using thresholds from near distance to far distance will make the familiar dendrogram. This dendrogram is equivalent to that often met in hierarchical clustering. (c) Once the regions are shuffled by ignoring the location, the horizontal segments of dendrogram can be aligned to be stacked which has been called as barcode of Betti-0 by topologists studying topological analysis and persistent homology of connectivity data

Finally, group features of connectomics of brain graphs consist of single matrices per group. Statistical comparison of these matrices should have been developed. The brute-force and easiest way was adopting permutation. Multiple comparison between permuted data matrices could also be performed to discover appropriate edges having statistical significances (Fig. 4). In brief, using the re-sampled distribution of maximum values (among the entire edges) of the differences of single linkage distances acquired from the virtual groups permuted 10,000 times, we determine the statistically significant edges between the observed two groups [30]. In this way, the multiple comparison problem of finding edges significantly different between normal controls and patients with neuropsychiatric disorders could be overcome. However, this was just the application of currently available statistical method to our goal of comparing groups' matrices in order to discover the edges responsible for the significant differences between groups. Investigators did not apply the FNDR minimization while controlling FDR especially using hidden Markov random

a Permuted virtual distribution of normal controls and ADHD on FDG PET



b Permuted virtual distribution of Audio -Visual (AV) task and control of Audio-Visual Noise task on fMRI

c Permuted virtual distribution of Remember and No-Remember trials on MEG

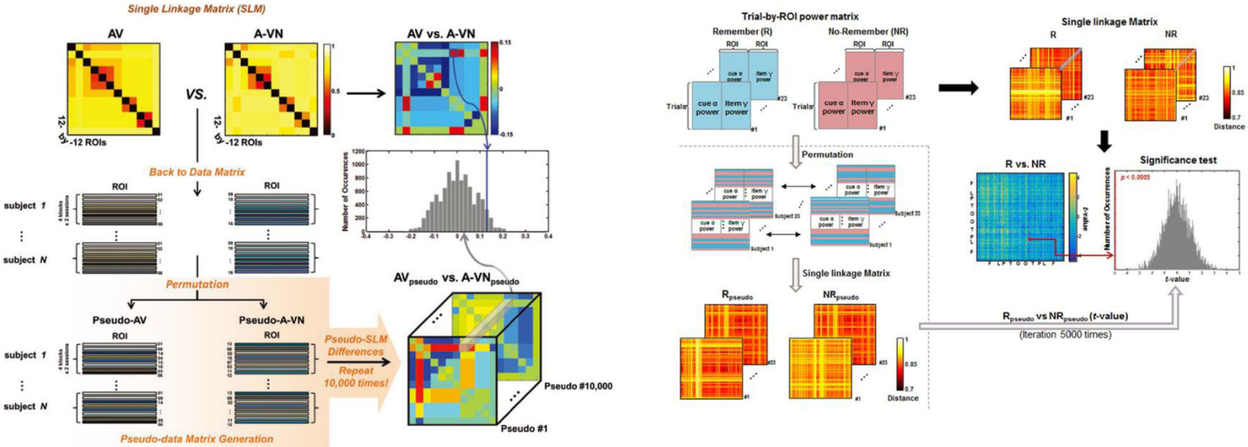


Fig. 4 Group comparison based on permutation of the group data by making virtual distribution using 10,000 times of iteration of mixing appropriate pairs. (a) Permuted distribution of normal and ADHD population was acquired by exchanging the subjects between normal and ADHD groups. Each permutation will produce one single linkage matrix and the repeated permutation usually 10,000 times makes 10,000 single linkage matrices. Single linkage distances contained in these single linkage matrices make distribution which are virtual based on permutation and act as norms to determine the observed single linkage distances are statistically significant to reject null hypotheses. (b) On the data of task-activation fMRI, permutation was done by exchanging audio-visual (AV) and audio-visual noise (A-NV) groups. Making distribution of single linkage distances using 10,000 times iterated permutation and production of single linkage matrices is the same as (a) (derived with exemption of permission for authors' reuse from Kim H, et al., Brain Connectivity 2015. ref. [15]). (c) On the data of MEG, post hoc finding of success of recall and failure of recall was used to designate groups of recall (R) and no recall (NR). These groups were permuted to yield single linkage matrices over trials and these single linkage matrices were used to make distribution. Observed single linkage distances of power of each ROI on alpha and gamma frequency ranges on wavelet transformed MEG signals were compared with these virtual distributions (derived with permission exemption with CC from Hahm J et al., Sci Rep 2017. Ref. [16]). ADHD attention deficit hyperkinetic disorder, MEG magnetoencephalography

field assumption [4, 5] and thus so far they are losing the information from their investigations, i.e., higher false negatives despite controlled false positives (< 0.05). This permutation worked well with FDG PET [13], activation fMRI [14], and MEG [15] data. The permutation method was also used to find the global differences between matrices of groups of comparison [13, 31, 32]. The matrices of virtual groups of mixing the data of two groups data permuted 10,000 times were put into the calculation of bottleneck or Gromov-Hausdorff distances and the observed distances were compared with this norm. Statistical inference finding the differences between groups was performed both for global differences and for connecting edge differences. Multiple comparison problem was more influential when we tried to find the edges of significant differences between groups statistically.

From Undirected Weighted to Directed Weighted Brain Graphs

So far, with apparently futuristic brain graphs based on cutting-edge network sciences, investigators did not define the metric spaces of brain graphs and spaces embedding these graphs. Only recently, few reports began to study the non-Euclidean nature of complex networks [33–35]. Determination of the curvatures of hyperbolic to Euclidean or even spherical geometry of global brain graphs and their local variations of the curvatures of mostly hyperbolic brain graphs would elucidate the real nature of the interregional brain networks in terms of local and regional and also global geometry [33, 34]. And also, investigators could not make trustworthy directed weighted brain graphs and probably because of this, they developed the methods of determining causality of information flow over the brain graphs, such as Granger causality (autoregressive vector modeling), dynamic causal modeling, or transfer entropy [36–38].

One can set up a model called generalized Markov system based on universal cover of brain graphs, estimate topological entropy of these brain graphs which is called volume entropy and calculate deterministically brain graph's volume entropy and edge capacity [39]. Once edge capacity was produced, one could calculate the inflow and outflow of each node and to calculate the node capacity. Final product of brain graph was directed weighted brain graph. On this directed weighted brain graph, as they could determine the node and the edge capacities, group comparison could be done using the similar permutation tests. Ten thousand times permuted virtual group data could yield the reference distribution of directed weighted graphs and the observed Gromov-Hausdorff distance was compared with the virtual distribution with correction for multiple comparisons. And also, the virtual distribution of edge or node capacity matrices could differentiate the statistically significant edges and nodes between groups. One could say now that certain nodes were different in their capacity and increased or decreased in their inflow or outflow from the controls. Transfer entropy or causality reasoning and their comparison between neuropsychiatric diseases and normal controls are to be examined. Psychometric data or clinical attributes are going to be correlated with this abnormality. Finally, this directed weighted brain graphs are going to be used as utilities to yield the information regarding the classification of diseases and the prediction of the clinical course onward from the time of initial evaluation.

Deep Learning Helps Elucidate Neuropsychiatric Diseases Using Brain Graphs

Despite popular use of VBM and SPM with strict control of type I error, the real problem resided in the missing controls. No investigators could overcome the problematic shortage of controls which would have been costly and time-consuming to produce. Such would be also the case with genomics, both in genome-wide association study (GWAS) and rare disease variant study [40]. Generative deep learning was proposed to solve this problem taking advantage of generative model's capability of missing data imputation [24]. This method was so far successful to make virtual normal population to take the role of controls to discover anomaly in the topography of FDG uptake on PET [25].

Degenerate images due to low-dose CT in PET/CT studies [41], absence of MRI as templates for amyloid PET studies [42, 43], or even PET without CT [44] could all be recovered by deep learning to generate high-resolution CT, to generate MRI template from amyloid PET images, or to generate attenuation map using transmission images, respectively. These successes raised much hope to tame the PET/CT and PET/MRI without taking further radiation burden or costly equipment. Though the catching-up follower investigators would not be able to proceed the empirical proof study, they can also use the simplified version of these studies immediately using publicly available algorithms. In fact, humans, by using human intelligence, already had long been using the information and would-be expertise, in order to recognize abnormality in topography on T1 MRI or on FDG or amyloid PET. They say that human intelligence is excellent in missing data imputation, good at using scanty data to reason further to find unrelated anomaly, and just best in transfer learning. Human experts do not care about the instruments (either a PET from one company or another PET from others), modality (either F-18 fluorbetaben PET, C-11 PIB PET or FDG PET), or even the age-related changes when they are going to designate certain abnormality which they just see for the first time.

These advantages are rapidly being followed by artificial intelligence (AI) with their novel deep learning algorithms. Human intelligence immediately recognizes also where the significant abnormality on MRI or PET is located, which AI investigators start to call explainable artificial intelligence (XAI) currently.

However, all that we now acknowledge as the help of AI are about the recognition of the topography on functional images of PET. Though the connectivity of regions of the brain and its contribution would have made the distribution of FDG uptake as is in the current pattern, deep learning algorithm of AI did not have, in its interior, the method how to analyze the connectivity of these regions. The connectivity should have been inferred by the appropriate statistics upon the repeated observation of resting-state fMRI in an individual or upon the varied image data acquired from a group of subjects which were assumed to be homogeneous and to show only the statistical variation. Modeling was imperative for interpreting the findings in these cases, i.e., distribution or normal distribution or even hierarchical general distribution of means and variances [3]. Topological characteristics have yet been beyond the reach of simple convolutional approach upon 2D or 3D topographical images of PET and MRI.

Perspective of Materialization of Personal Connectomics of Hybrid PET/fMRI

As was explained above, topological approach to the interpretation of brain connectivity solved several problems of arbitrariness, comparison of global differences between groups and localization of discriminative interregional connectivity in certain groups of brain disorders [13, 31]. And also, the limitation of topographic understanding of gray matter density (T1 signal), BOLD signal (fMRI), and glucose metabolism (FDG uptake) in the elaboration of connectivity of the brain regions is currently evident both theoretically on principle and practically on reports and data in the literature. By the way, clinical use of brain connectomics will be made possible only by simple and straightforward use of any imaging instruments or software including deep learning algorithms. Data might be important in the beginning to prove empirically the validity of the simplified methods with imputed missing data along the life epochs of development and aging while elucidating demographic influences of subtle differences. Hybrid PET/MRI might be used for this purpose (Fig. 5).

PET was initially used as proof-of-concept study to suggest its practical efficacy to clarify the inherent connectivity between regions based on population data; interestingly however, the number of subjects were small (controls 10, disorder groups, around 30 each) [13], but they could delineate the global difference and unravel the differences of autism and attention deficit hyperkinetic disorder (ADHD) from normal children. More interesting was that they used only the information of 0-dimension, i.e., Betti-0 or number of connected components. They further used dendrogram and minimum spanning tree or knitting-ball gram but still confined the analysis to 0-dimensional characteristics [14–16]. Higher dimensional interpretation of simplicial chain complex of brain graphs remains and 1-cycle or 1-hole interpretation is at the beginning now [45–47]. Avoiding the arbitrariness of thresholding, by making single linkage matrices, the analysis equaled the analysis looking into all-the-threshold examination. We need to be reminded that PET connectomics were from the population of homogeneity assumption within the population.

By paying attention to the global information flow of brain graphs, they could also define volume entropy, topological entropy of n-1 sphere of n-ball of universal covering tree made of brain graph of interest, and were able to make directed weighted brain graphs made of the nodes and edges with designated capacities at that moment of observation on resting-state fMRI or FDG PET [39]. Of course, here again resting-state fMRI was showing the directed weighted brain graph of BOLD signal amplitudes of 5 min of observation period in the scanner. On the contrary, FDG PET yielded directed weighted brain graph of FDG uptake assuming that the observed group of subjects are homogeneous in terms of interregional connectivity of brain regarding glucose metabolism. Anyone can conceive the idea of combining these two information derived from a hybrid machine. This goal can be achieved with several limitations or assumptions to ignore these limitations.

The first one is physiological. FDG PET is producing the information as brain images representing the period of brain activity after injection of FDG until image acquisition, almost 40 min to 1 h. This is outside of the scanner and subjects used to be comfortable with drifting thoughts. Resting-state fMRI is acquired during imaging in the scanner gantry of hybrid PET/MRI, which is really noisy, alerting and uncomfortable for most of the subjects undergoing image acquisition. However, encouraging was that despite the repeating experiences of imaging familiarization to these experiences did not cause much discernible changes in the participating components of a subject's brain even with 158 scanning spanning 3 or more years [7]. This stability of human brain to run resting-state activity encourages us to move forward to combine PET and resting fMRI. It is already known that FDG PET studies yield consistent results on repeated imaging.

The second one is the variation of the connectomes among individuals which was taken by resting-state fMRI and analyzed by the cutting-edge method of producing

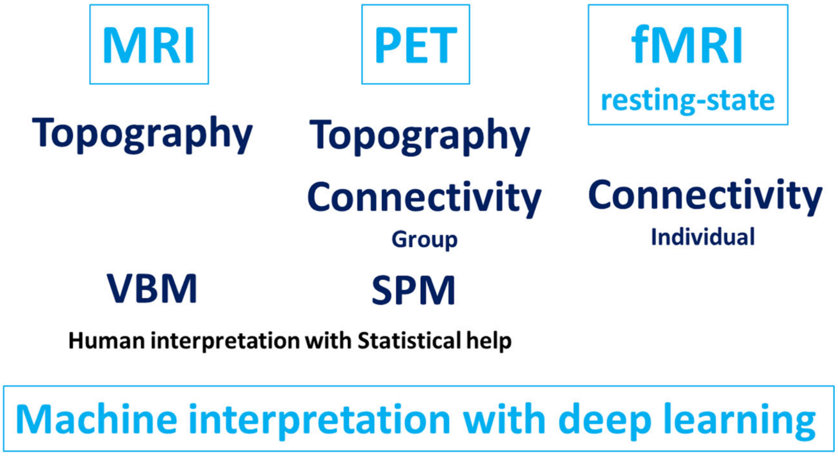


Fig. 5 Brief summary of PET/resting-state fMRI and their outputs of information regarding brain glucose metabolism on FDG PET or BOLD (blood oxygen level dependent) signal on resting-state fMRI. Structural MRI (their T1 images) is analyzed using voxel-based dosimetry (VBM) and FDG PET is analyzed using statistical parametric mapping (SPM). Both MRI and PET produce single images for individuals and unravel the topography (distribution pattern) of T1 signal density and FDG uptake, respectively. PET can also make metabolic connectivity available over the group examination (over the subjects); however, fMRI makes connectivity based on BOLD signal amplitudes of usually 100 3-s trials in each individuals. VBM, SPM, or connectivity data are now analyzed by humans or if needed and feasible by machines. Machine interpretation of these images with deep learning can now be expected

directed weighted brain graphs [39, 48–50]. Once the variation is high, investigators might need to classify and interpret the meaning of these variations and also devise novel method to determine the commonality of connectivity mimicking the methods to have defined the authentic independent components of longitudinal or population studies explained above.

The third one is the correlation job to find the relationship between resting-state fMRI and FDG PET. This immediately implies that individual connectomes derived from resting-state fMRI will be associated with topographic distribution of FDG uptake of PET. Topological description of BOLD connectomes are to be associated with topographical distribution of glucose metabolism. In this endeavor, there still remains two problems and assumptions to ignore these two. One is the coupling between topology and topography. In the above, I elaborated that this was not appropriate due to many theoretical and practical reasons, but I say here now, on the contrary, for clinical application of personal connectomics on PET/MRI, we need to associate these two in an ingenious way. I also explained that the current version of deep learning, how much deep it had been, does not seem to be helping the progress. The chasm between topography and topology would be so deep and wide as abyss to deter our future efforts to overcome this problem, but it is sure to be solved. Another is the coupling between perfusion and metabolism, more fundamental as an assumption. We have continuously assumed that BOLD represents the brain's cognitive activity very nicely though there were scattered challenging complaints [51–55]. Entire community of cognitive neuroscience and human brain mapping have been ignoring the possibility of existing status of brain showing less-tight coupling of perfusion and electrical activities or even uncoupling thereof. We continue to follow this assumption and only when the data from two modalities FDG PET and BOLD resting-state fMRI do not match seriously, we will look back the possibility of uncoupling.

Deep learning community recently attended keenly to improve their job by adopting relational information of images of interest, which is counterpart of connectivity of the human brain. We need to wait for the progress and will immediately import the success of deep learning community, if any, to connectomics works. 3D expansion of CNN or related algorithm or stability issues of generative adversarial network (GAN) are still facing an inherent computing load problem or mode collapse problem, respectively, and soon will be overcome [56]. Most notably, the successful training of AlphaGo Zero by AlphaGo was again encouraging [57]. Though how deep the chasm or how high the obstacle is in an effort to associate topographical FDG PET and topological resting-state fMRI, we wish we will overcome this bottleneck as was the previous occasion when we succeeded in adopting topology.

Summing up, successful topographical analysis of brain images could not replace connectivity analysis in the past. Now, as connectivity analysis can unravel how the brain works in group (PET) and in individuals (resting-state fMRI), connectivity represented by topological analysis (resting-state fMRI) shall be matched again with topographical characteristics of brain image in individuals (PET). Topographical PET in individuals and interpreted fMRI connectivity by topology in group and connecting this with generative deep learning will make hybrid PET/fMRI produce personal connectomics soon.

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Compliance with Ethical Standards

Conflict of Interest Dong Soo Lee declares that there is no conflict of interest.

Ethical Approval All procedures performed in studies were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent As a review article, obtaining informed consent was waived.

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