



HAL
open science

The multiscale topological organization of the functional brain network in adolescent PTSD

David Corredor, Shailendra Segobin, Thomas Hinault, Francis Eustache,
Jacques Dayan, Bérengère M Guillery-Girard, Mikaël Naveau

► To cite this version:

David Corredor, Shailendra Segobin, Thomas Hinault, Francis Eustache, Jacques Dayan, et al.. The multiscale topological organization of the functional brain network in adolescent PTSD. *Cerebral Cortex*, 2024, 34 (6), pp.bhae246. 10.1093/cercor/bhae246 . hal-04616062

HAL Id: hal-04616062

<https://hal.science/hal-04616062>

Submitted on 18 Jun 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

The multiscale topological organization of the functional brain network in adolescent PTSD

David Corredor^{1,*}, Shailendra Segobin¹, Thomas Hinault¹, Francis Eustache¹, Jacques Dayan^{1,2}, Bérengère Guillery-Girard¹, Mikaël Naveau³

¹Centre Cyceron, CHU de Caen, Neuropsychologie et Imagerie de la Mémoire Humaine, Normandie Université, UNICAEN, PSL Université Paris, EPHE, INSERM, U1077, Caen 14000, France

²Pôle Hospitalo-Universitaire de Psychiatrie de l'Enfant et de l'Adolescent, Centre Hospitalier Guillaume Régnier, Université Rennes 1, Rennes 35700, France

³UNICAEN, CNRS, INSERM, CEA, UAR3408 CYCERON, Normandie Université, Caen 14000, France

*Corresponding author. Normandie Université, UNICAEN, PSL Université Paris, EPHE, INSERM, U1077, Centre Cyceron, CHU de Caen, Neuropsychologie et Imagerie de la Mémoire Humaine, Caen, France. Email address: david.corredor@helsinki.fi

The experience of an extremely aversive event can produce enduring deleterious behavioral, and neural consequences, among which posttraumatic stress disorder (PTSD) is a representative example. Although adolescence is a period of great exposure to potentially traumatic events, the effects of trauma during adolescence remain understudied in clinical neuroscience. In this exploratory work, we aim to study the whole-cortex functional organization of 14 adolescents with PTSD using a data-driven method tailored to our population of interest. To do so, we built on the network neuroscience framework and specifically on multilayer (multisubject) community analysis to study the functional connectivity of the brain. We show, across different topological scales (the number of communities composing the cortex), a hyper-colocalization between regions belonging to occipital and pericentral regions and hypo-colocalization in middle temporal, posterior–anterior medial, and frontal cortices in the adolescent PTSD group compared to a nontrauma exposed group of adolescents. These preliminary results raise the question of an altered large-scale cortical organization in adolescent PTSD, opening an interesting line of research for future investigations.

Key words: adolescent PTSD; whole cortex functional connectivity; multisubject networks; community detection; resting state functional Magnetic Resonance Imaging.

Introduction

Noninvasive brain imaging techniques allowing the investigation of brain architecture and dynamics in vivo and in real-time have become a central and promising tool to understand the neural consequences of exposure to a potentially traumatic event. An open topic in clinical neuroscience is why and how, after experiencing an extreme aversive event, some people might develop (or exacerbate) a maladaptive cerebral and behavioral profile and the manifestation of posttraumatic stress disorder (PTSD) symptoms or other trauma-related pathologies. Although definitive brain signatures are still missing, in the last decades, technological developments in brain imaging and sophistication in data-analysis pipelines have provided important results on the brain alteration accompanying trauma exposure and PTSD.

Initial results from animal models and early activation paradigms using symptom provocation or trauma-related images showed that the amygdala, the medial prefrontal cortex, and the hippocampus are critical brain regions in PTSD appearance and symptomatology (Shin et al. 2006; Pitman et al. 2012). Subsequently, with the increased use of the resting state paradigm and the discovery of the organization of the cerebral cortex in intrinsic networks (INs) (for review, see Uddin et al. 2022; Uddin et al. 2019), the focus on the activation of specific regions

was completed by large-scale brain analysis in PTSD (Ross and Cisler 2020). Investigations of the connectivity profile between a region of interest (ROI) and the rest of the brain (i.e. seed-based analysis) showed an altered large-scale brain organization in PTSD involving regions from the default mode (DMN), salience, and control networks (Ross and Cisler 2020).

Seed-based analysis requires the selection of a priori regions of interest and overlooks brain regions and connections outside the direct connections with the selected ROI. However, it has been shown that the brain is a complex system (Avena-Koenigsberger et al. 2018; Sporns 2011; Thiebaut de Schotten and Forkel 2022), meaning that its functional properties arise from the interaction among its constituents, including indirect connections between regions. In this vein, recent studies using a whole-cortex approach, without the a priori selection of ROIs, presented complementary results to the activation and seed-based approaches in PTSD (Misaki et al. 2018; Breukelaar et al. 2021; Shaw et al. 2023).

Importantly, the exposition to extreme aversive events can arrive early in life, with a particular propensity during adolescence (McLaughlin et al. 2013). The high rate of trauma exposition during childhood and adolescence leading to the potential development of PTSD and the associated impairments in daily life requires the investigation of the neural consequences

Received: January 4, 2024. Revised: May 17, 2024. Accepted: May 18, 2024

© The Author(s) 2024. Published by Oxford University Press.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

of trauma exposure during youth (Marshall 2016; Cisler and Herringa 2021). Although in recent years increased consideration has been paid to the neural specificities of trauma exposure and PTSD during adolescence (Leibenluft and Barch 2021), this population remains largely understudied in clinical neuroscience. Similar to adult PTSD, the majority of investigations on adolescent PTSD have been conducted using activation or seed-based analysis showing alterations in their functional brain organization (for a review, see Cisler and Herringa 2021; Ross and Cisler 2020). Though relevant, this “one-to-many” approach overlooks potentially relevant brain regions and connections. To our knowledge, no study has investigated the whole-cortex “many-to-many” organization in adolescents with a clinical diagnosis of PTSD.

This exploratory work aims to fill this gap by studying the functional brain organization in 14 adolescents presenting a clinical diagnosis of PTSD from a whole-cortex perspective. To do so, we built on the network neuroscience framework, specifically in community analysis (Betzler 2020). We use the multisubject community detection (MSCD) method (Betzler et al. 2019) to compare the community (also known as module or subnetwork) organization in functional brain data between a group of nontrauma exposed adolescents and a group of trauma-exposed adolescents presenting severe PTSD symptoms.

We show the capacity of the MSCD to detect differences in the functional organization between the control and PTSD groups at the global, whole-cortex organization (i.e. the difference in the community organization), and at the local pairwise connections between brain regions. Importantly, complementary to approaches using an a priori allocation of brain regions to functional subnetworks where each region exclusively belongs to one subnetwork, we present results across three topological scales (i.e. the number of unraveled communities composing the cortex), allowing a richer characterization of the composition and interaction of whole-cortex functional subnetworks, expanding previous results in both adult and adolescent PTSD. Furthermore, instead of allocating brain regions to previously defined functional networks (e.g. the Yeo subnetworks; Yeo et al. 2011), the use of a data-driven method tailored to our population of interest circumvents the overreliance on subnetwork construction based on healthy adult information.

Consistent with previous results, across topological scales, communities are organized in accordance with the large-scale unimodal-transmodal (Margulies et al. 2016; Vázquez-Rodríguez et al. 2019; Shafiei et al. 2020) and INs (Uddin et al. 2019) brain organization. When realizing group comparisons, a convergent pattern of results across topological scales points to (i) an increased co-localization between regions belonging to occipital and pericentral regions and (ii) a reduced co-localization between middle temporal, posterior–anterior medial, and frontal cortices in the PTSD group. The elucidation of the reasons behind the disparity in the functional organization between PTSD and nonexposed adolescents found here opens up an interesting line of investigation to better understand PTSD.

Methods

We present a novel analysis and results using a clinical data set that has been previously published. Details of the participants, clinical assessments, and neuroimaging data acquisitions can be found in (Viard et al. 2019) and are briefly summarized below.

Experimental dataset and data acquisition

Fifteen adolescents with PTSD, aged 13 to 18 years old, were recruited. Data of one patient were unusable because she slept during the resting state functional Magnetic Resonance Imaging (fMRI) scan. All presented chronic PTSD for at least 6 months. Twenty-four typically developing adolescents with no history of trauma were chosen to match the patient group regarding age and IQ. Altogether, 14 PTSD patients (12 females) and 24 controls (13 females) were included in the analyses (for more details, see Viard et al. 2019). The study was approved by the local Ethics Committee (CPP Nord Ouest III). All adolescents and their parents signed informed consent after a comprehensive description of the study.

All participants were scanned with a Philips Achieva 3.0 T MRI scanner at the Cyceron Center (Caen, France). High-resolution T1-weighted anatomical volumes were acquired using a 3D fast-field echo sequence (3D-T1-FFE sagittal; repetition time = 20 ms, echo time = 4.6 ms, flip angle = 10°, 180 slices, slice thickness = 1 mm, field of view = 256 × 256 mm², in-plane resolution = 1 × 1 mm²). Resting-state fMRI functional volumes were obtained using an interleaved 2DT2* SENSE EPI sequence designed to reduce geometric distortions with parallel imaging (2D-T2*-FFE-EPI axial, SENSE = 2; repetition time = 2382 ms, echo time = 30 ms, flip angle = 80°, 42 slices, slice thickness = 2.8 mm, field of view = 224 × 224 mm², in-plane resolution = 2.8 × 2.8 mm², 280 volumes). The resting state fMRI duration was 11.26 min.

Data preprocessing and subject functional co-activity network

Functional data were preprocessed using the CONN toolbox release 22.a (<https://web.conn-toolbox.org/>) and the Statistical Parametric Mapping toolbox (SPM 12, University College London, London, UK). Functional images were realigned to the first volume, slice-timing corrected, normalized into standard MNI space, and smoothed with a Gaussian filter kernel of 8 mm width half maximum. Noise components from cerebral white matter and cerebrospinal areas, subject-motion parameters, scan outliers constant, and first-order linear session effects were entered as confounds in a first-level analysis. In the main analysis, acquisitions with framewise displacement (FWD) above 0.9 mm or global BOLD signal changes above 5 SD were taken as noise components, used as potential confounding effects, and regressed from the final time series. No subject had 20% or more volumes flagged as noise components. Therefore, we used the entire cohort for subsequent analyses. Finally, a temporal band-pass filter (0.01–0.1 Hz) was applied. The preprocessed time series for each brain region was used to create the subject’s functional networks.

Here, we defined the network nodes using the 91 regions of the Harvard–Oxford parcellation, expanding the whole cortex. Furthermore, for their known relevance in PTSD pathology, we also included the bilateral amygdala and hippocampus from the subcortical Harvard–Oxford parcellation. Altogether, functional networks were summarized as adjacency matrices $W = [w_{ij}]$, $ij \in [1, 95]$ whose entries correspond to Z-transformed Pearson’s correlation coefficients between the pairwise time series of the 95 nodes. We kept signed coefficients without thresholding.

We re-run the analyses using the Brainnetome parcellation to assess methodological robustness. The Brainnetome atlas comprises 246 regions, from which we selected all cortical regions plus the amygdala and hippocampus, resulting in 218 regions. Furthermore, to assess the possibility of spurious results due to in-scan movement or the sex ratio imbalance between the PTSD

and control group, we re-run the analysis using a “conservative” setting with FWD > 0.5 mm and > 3 SD of global BOLD signal changes as thresholds for flagging noise volumes. Next, we built the multilayer networks containing the same female/male ratio randomly selecting for each iteration 12 females and two males (among the 24 subjects) in the control group. Results and figures for the Brainnetome Atlas and quality control checks can be found in the [Supplementary Document](#).

Community detection

Community detection applied to fMRI is a data-driven method to identify brain communities based on the functional connectivity (FC) network of each subject (i.e. single-layer community detection [SLCD]). In SLCD, a network is clustered by maximizing an objective modularity function by quantifying groups of nodes more connected to each other than expected in an appropriate null model (Betzel 2020). To perform group comparisons, SLCD is applied to each subject’s FC matrix, allowing the subject information to be kept but at the risk of overfitting (Betzel et al. 2019). Otherwise, it is necessary to create an averaged connectivity matrix for each group and use SLCD to unravel its community structure, decreasing the risk of overfitting but blurring subject-specific information.

Multisubject community detection

A method providing a trade-off between group-level and subject-level community detection comes from an extension of the SLCD dealing with multiple networks simultaneously (i.e. multilayer networks) (Mucha et al. 2010). A multilayer network is a convenient representation for directly relating different levels of a dataset in a single mathematical construct (Artibe et al. 2022). In neurosciences, multilayer networks have been used to study the functional organization of the brain across time windows in a single fMRI acquisition, the functional re-organization across different tasks, and the relationship between different neuroimaging modalities (for review, see Vaiana and Muldoon 2020). Importantly, this method has been recently used to relate FC matrices of different subjects (Betzel et al. 2019). This implementation is formalized in a categorical multilayer network, where homologous nodes in the network across all layers are connected. In this case, each brain region is connected to its counterpart region across all subjects in the multilayer (multisubject) network. Layers in the multisubject network correspond to the FC matrices of subjects. In the present work, for the first time, we extended this approach to a clinical investigation to compare the functional organization between a group of adolescents with a diagnosis of PTSD and a group of nontrauma exposed adolescents.

Similar to SLCD, MSCD relies on the maximization of the modularity function (equation 1). Therefore, as in the single-layer case, in MSCD, it is necessary to specify a null model and the resolution parameter (γ). Moreover, it is also required to precise the value of a second parameter controlling the interlayer strength coupling (ω) (eq., 1).

$$Q(\gamma, \omega) = \sum_{ijsr} [(W_{ijs} - \gamma P_{ijs}) \delta_{sr} + \omega \delta_{ij}] \delta(\sigma_{is} \sigma_{jr}) \quad (1)$$

With:

- i, j network nodes;
- s, r network layers;
- W_{ijs} weight of the edge linking nodes i and j in layer s ;

- γ spatial resolution parameter (gamma);
- P_{ijs} weight of the edge linking nodes i and j in layer s in the null model;
- ω interlayer strength parameter (omega);
- $\delta_{sr} = 1$ if $s = r$; 0 otherwise
- $\delta_{ij} = 1$ if $i = j$; 0 otherwise
- σ_{is} community of node i in layer s
- $\delta(\sigma_{is} \sigma_{jr}) = 1$ if $\sigma_{is} = \sigma_{jr}$; 0 otherwise

Because we work with correlational networks, we use $P_{ijs} = 1$ as the null model in the modularity function (Bazzi et al. 2016; Betzel et al. 2019).

For every iteration of the MSCD, we randomly selected 14 (among the 24) control subjects to build a balanced multilayer network regarding the number of subjects per group. Hence, the input of the MSCD is a multilayer network composed of 28 layers corresponding to the pairwise functional brain co-activity of 95 regions from the 14 PTSD subjects plus 14 control subjects (Fig. 1A).

Partition selection

After one iteration of the MSCD, we obtain a multisubject partition matrix containing information about community membership for each node and subject in which rows correspond to brain regions and columns to subjects (Fig. 1A). The combination of γ and ω parameter values in the modularity function produces different partitions regarding the number of communities and the similarity of partitions across subjects. Thus, the landscape of possible multisubject partitions can be organized according to the partitions’ topological scale (i.e. the mean number of communities) and flexibility (Betzel et al. 2019). In other words, multisubject partitions can go from one single community to n communities (n = number of regions in the network) and have a flexibility value from 0 (partitions are identical across subjects) to 1 (partitions are totally different).

To run group comparisons, we start by filtering out multisubject partitions obtained across iterations of the MSCD based on their flexibility and number of communities. First, we required comparable but not identical partitions across subjects to obtain a coherent group partition while keeping subject specificities. Thus, we excluded partitions with extreme flexibility values, keeping multisubject partitions with flexibility values within the range [0.2:0.8]. Second, based on Betzel et al. (2019), we excluded partitions with more than 20 communities, keeping partitions with a mean number of communities within the range [2:20], allowing us to investigate different topological scales of the brain functional organization.

We ran the MSCD algorithm with randomly selected pairs of γ and ω values until we obtained 10,000 multisubject partitions within the previously defined flexibility and number of community boundaries (for details about these partitions, please see the [Supplementary Information Document](#) and [Supplementary Fig. 1](#)). Among this initially constrained set, we kept topological scales presenting the most stable organization (lower value in the average variation of information across partitions and iterations of the algorithm) for further analysis. Based on the variation of information ([Supplementary Fig. 2](#)), we selected partitions composed of [2–4] communities (first topological scale), [5–7] communities (second topological scale), and [12–14] communities (third topological scale). Among the 10,000 partitions, the first topological scale represents 1,919, the second 3,486, and the third topological scale 934 partitions.

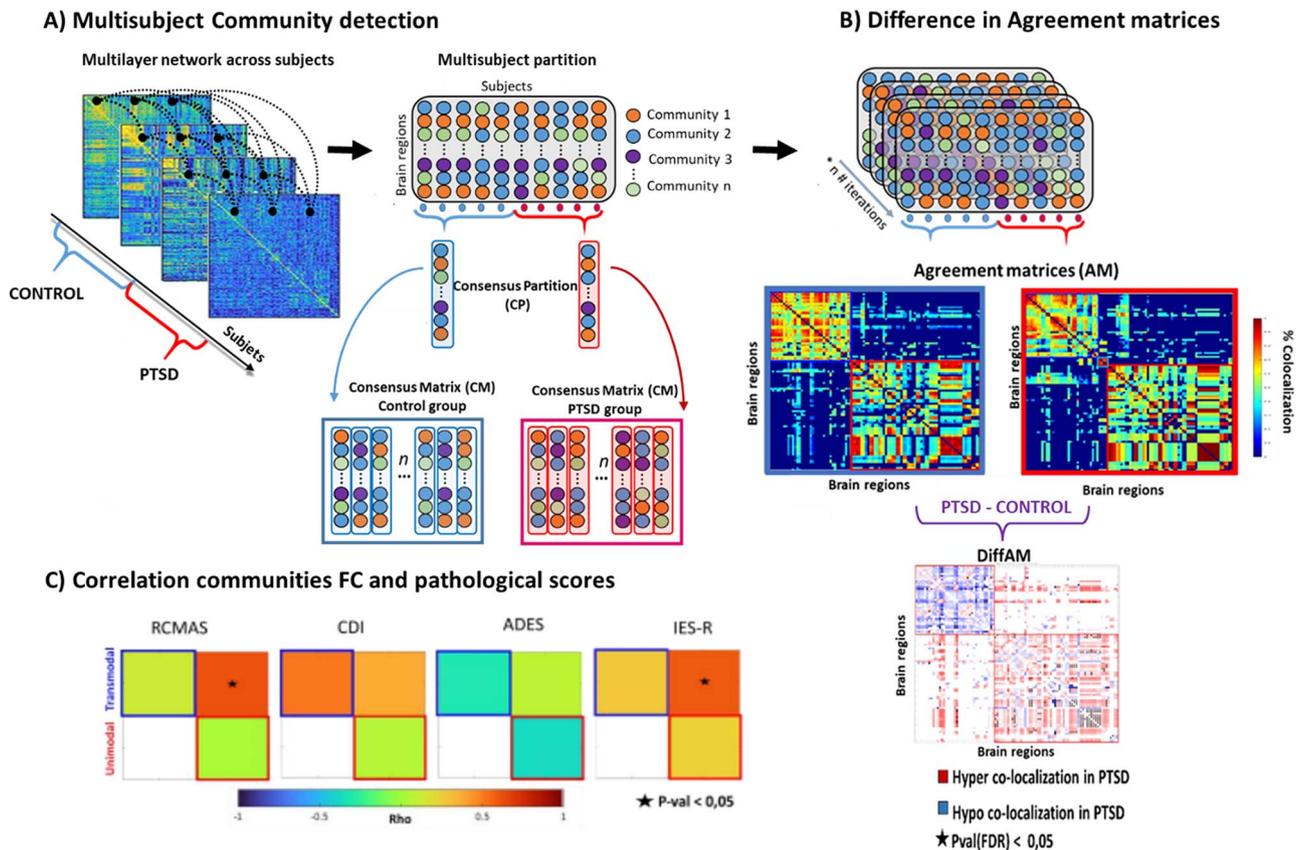


Fig. 1. MSCD procedure. **A)** A multilayer network comprising 14 PTSD and 14 control subjects was subjected to a modularity maximization procedure to determine subjects' partitions, summarized in the multisubject partition. For each group, we computed the consensus partition (CP) as the mode of a given region across subjects. We iterated this procedure multiple times to control for the degeneracy in the community detection algorithm and sweep across topological scales. We computed the CPs for each iteration of the MSCD and computed the similarity of CPs across iterations for each group. **B)** Example for one topological scale: We calculated the Agreement Matrices (AM) representing the frequency at which any two nodes were assigned to the same community across subjects and iterations. We computed the difference between the AM of the two groups (DiffAM). In the DiffAM, entries >0 (red) correspond to pairs of nodes that are more co-localized (hyper-co-localized) in the PTSD group compared to the control group. Entries <0 (blue) correspond to hypo-co-localized nodes in the PTSD group compared to the control group, and entries equal to zero (green) denote no difference between groups. **C)** Finally, we went back to the functional connectivity (FC) matrices of PTSD subjects to calculate the correlation coefficients (ρ) between FC and pathological scores (RCMAS: revised children's manifest anxiety scale; CDI: Childhood depressive intervention; ADES: the adolescent dissociative experience; IES-R: the symptom severity scale).

Communities' analysis

For each iteration of the MSCD, a consensus partition is computed as the mode of community assignment across subjects for each brain region (Betzel et al. 2019) (Fig. 1A). By splitting the subjects according to group membership (i.e. control, PTSD), we obtained a consensus partition for each group. Then, for each topological scale, we summarized all iterations of the MSCD in a consensus matrix of dimensions $[n \times i]$, where n is the number of brain regions, and i is the number of partitions (Fig. 1A). We used the consensus matrix to test the representability of the partitions for each group. To do so, we assessed whether group partition similarities were higher within the control and PTSD groups than in two random groups constituted of a mixture of control and PTSD subjects (see section 2.8).

Pairwise analysis

To investigate the node-to-node specificities in brain organization, we compared the frequency at which any two nodes were allocated to the same community, summarized in the so-called Agreement matrix. In functional brain studies, it has been shown that agreement matrices contain critical information that is not accessible when solely studying FC matrices (Bassett et al. 2015).

For each group, we computed an agreement matrix (AM) summarizing information across all the partitions within the specific topological scale (Fig. 1B). The AM is a symmetric $n \times n$ matrix ($n = 95$ brain regions), representing the number of times, across the 14 subjects and the number of iterations, two nodes were assigned to the same community, divided by the maximum number of times they could be together. To control for spurious pairwise associations, we thresholded the AM matrices following the procedure in Bassett et al. (2013).

To compare the groups, we subtracted the AM of PTSD subjects from the AM of the control group (DiffAM) (Fig. 1). In this new matrix, entries equal to zero denote no difference between groups. Entries >0 correspond to pairs of nodes that are more co-localized (hyper-co-localized) in the PTSD group compared to the control group (Fig. 1 red entries in DiffAM). Entries <0 correspond to hypo-co-localized nodes in the PTSD group compared to the control group (Fig. 1 blue entries in DiffAM).

Result significance

To compute statistics, we run 10,000 times the analysis described in sections 1.6 and 1.7 using permuted versions of subjects' group identities to create an empirical null distribution

(Alexander-Bloch et al. 2012; Puxeddu et al. 2020). For each permutation, we reorganized the set of multisubject partitions according to a 1*28 vector of random subject labels (two groups of 14 subjects, each with a random mix of control and PTSD subjects). We compute the P -value as the number of times across permutations that the permuted data has greater differences between groups than the “real” data divided by the total number of permutations (10,000). Results were corrected using false discovery rate with a threshold of $P < 0.05$.

Group partition and visualization

We computed the representative partition for each group and each topological scale corresponding to the consensus partition that presents the mean lower distance (higher similarity) among all consensus partitions (runs of the MSCD).

Correlation with pathological scores

We investigated whether the information in the unraveled communities was correlated with pathological scores associated with PTSD. To do so, we returned to the FC matrices of the PTSD participants and computed, for each topological scale, the within and between FC strength for each community in the representative partition of the PTSD group. We used screening tests of pediatric symptoms: the revised children’s manifest anxiety scale, childhood depressive intervention, the adolescent dissociative experience, and the symptom severity scale.

Results

Communities composition across topological scales:

For both groups and atlases, the multiscale partitions were composed of distinct communities mirroring previous results concerning the fundamental brain functional organization. Figures 2 and 3 show the communities for the control and PTSD groups using the Harvard–Oxford Atlas (partitions using the Braintome Atlas can be found in the [Supplementary Document, Fig. 6](#)). To better visualize the community organization in the third topological, see Fig. 3.

In the first topological scale (Fig. 2, top left), the partition of the control group was composed of two communities. The first community (blue in Fig. 2, top left) contains brain regions of the frontal, middle temporal, and posterior–anterior medial cortices. The second community (red in Fig. 2, top) comprises occipital and pericentral brain regions. In the PTSD partition (Fig. 2, bottom left), there was a third community comprising the hippocampal complex (light blue in Fig. 2, bottom left).

For the second topological scale and the control group (Fig. 2, top middle), the two communities in the first topological scale split into five communities corresponding to frontal and middle temporal cortices (blue in Fig. 2, top middle), medial temporal regions (light blue), dorsal frontoparietal (green), pericentral (red), and occipital (pink), respectively. For the PTSD group, a small community comprising the precuneus and the posterior cingulate cortex appeared. Furthermore, the medial frontal and subcallosal cortex were allocated with the medial temporal regions and not in the frontal and lateral community, as in the control group.

Finally, in the third topological scale (Fig. 2, top right), we found 12 communities (singletons excluded) containing medial frontoparietal (two communities, dark blue), medial anteroposterior (one community, blue), medial temporal (two communities, light blue), lateral frontoparietal (three communities orange), dorsal frontoparietal (green), midcingulo-insular (yellow), pericentral

(red), the occipital (pink), and singletons communities (with single nodes; gray). For the PTSD group, we found ten communities (singletons excluded) similar in composition to the control group.

Partitions are group dependent:

We found a significant effect of group organization on the computation of group partitions for the first topological scale ($P = 0.002$), the second topological scale ($P = 0.005$), and the third topological scale ($P = 0.001$).

Hyper- and hypo-colocalized nodes in the posttraumatic stress disorder group:

To determine hyper-colocalized or hypo-colocalized nodes in the PTSD group compared to the control group, we used the difference between the two groups of the frequency at which any two nodes were allocated to the same community (Fig. 1). We found a set of hyper-colocalized nodes (red edges in Fig. 4 and [Supplementary Figs. 7, 8, 9](#)) in the occipital and pericentral communities for the three topological scales and both atlases. Moreover, we found a set of hypo-colocalized nodes (blue edges in Fig. 4 and [Supplementary Figs. 7, 8, 9](#)) in the frontal, lateral, and medial anteroposterior communities.

Correlation with pathological scores

After correcting for multiple comparisons, no significant correlations were found between FC metrics and pathological scores. Please see the [Supplementary Document](#) for the trends in the results.

Discussion

In the current exploratory study, we adapted the MSCD technique for the first time to a clinical population. In doing so, we studied, in a data-driven way, the multiscale functional topological organization of diagnosed adolescents with PTSD. This way, we examined the functional brain network without selecting a subset of ROI and unconstrained by adult functional templates (i.e. the communities’ composition). In doing so, we were able to highlight population-specific characteristics of adolescent PTSD beyond commonly associated brain regions and subnetworks. Furthermore, using the MSCD, we acquired information on the specificities in the network organization in adolescent PTSD across three topological scales. Although requiring replication in a larger cohort (see limitations section), the preliminary results obtained here raise the question of an altered large-scale cortical organization in adolescents with PTSD, opening an interesting line of research for more powered future studies.

An altered global organization in adolescents with posttraumatic stress disorder

For both control and PTSD groups, the multiscale partitions were composed of distinctive communities mirroring previous results concerning the fundamental brain’s functional organization along the unimodal-transmodal gradient (Mesulam 1998; Huntenburg et al. 2018; Shafiei et al. 2020) on which specific brain regions (and INs) are positioned (Margulies et al. 2016).

In the first topological scale, communities reflect a clear distinction between unimodal and transmodal regions (Margulies et al. 2016; Mesulam 1998; Preti and Van De Ville 2019; Shafiei et al. 2020; Vázquez-Rodríguez et al. 2019) (Fig. 2, top). A transition from this bimodal organization towards the subnetworks organization was observed at the second topological scale. Then, in the third topological scale, communities align with canonical INs

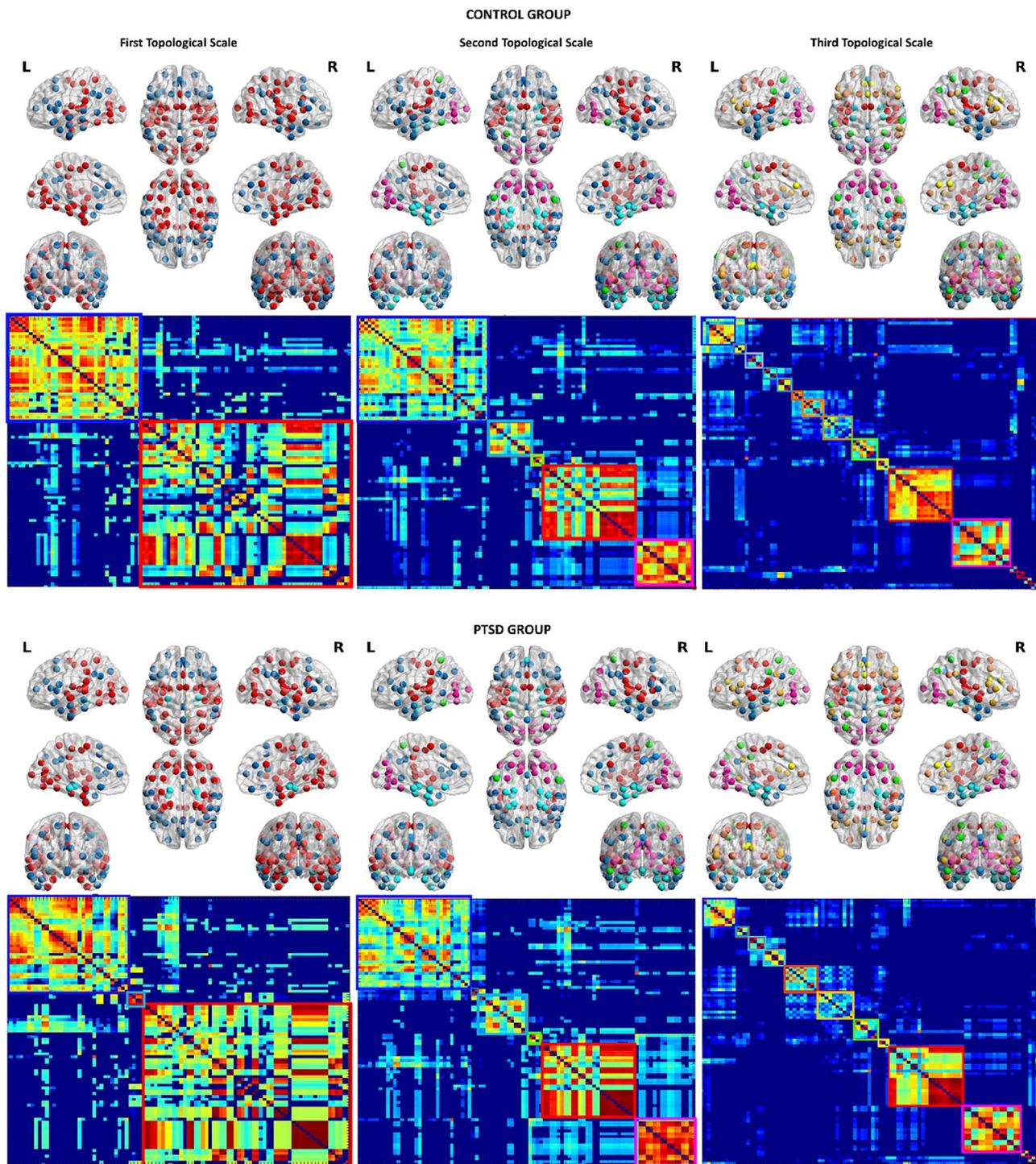


Fig. 2. The whole-brain multiscale community organization. Representative partition of the control group (top) and PTSD group (bottom) for the first (left), second (middle), and third (right) topological scales. Colors in brain plots and boxes in agreement matrices denote community affiliation.

(Yeo et al. 2011; Uddin et al. 2019) (Fig. 3). See Table 1 and the Supplementary Document for a description of the nodes belonging to each community.

The fact that partitions were more similar within than between groups shows that partitions were representative of each group and supports the observation of a different global, whole-cortex, functional organization in adolescent PTSD compared to controls. Despite the heterogeneity in the adolescent population with PTSD regarding age, severity of symptoms, type of trauma, or age of trauma, our results show a sensitivity of the MSCD to capture

specificities in this clinical population compared to the control group.

An altered pattern in the pairwise organization in adolescent with posttraumatic stress disorder (PTSD)

To identify the specificities of PTSD, we compared the pairwise functional organization between the two groups. To do so, we used the information in the Agreement matrices which are an extension of FC measures containing critical information

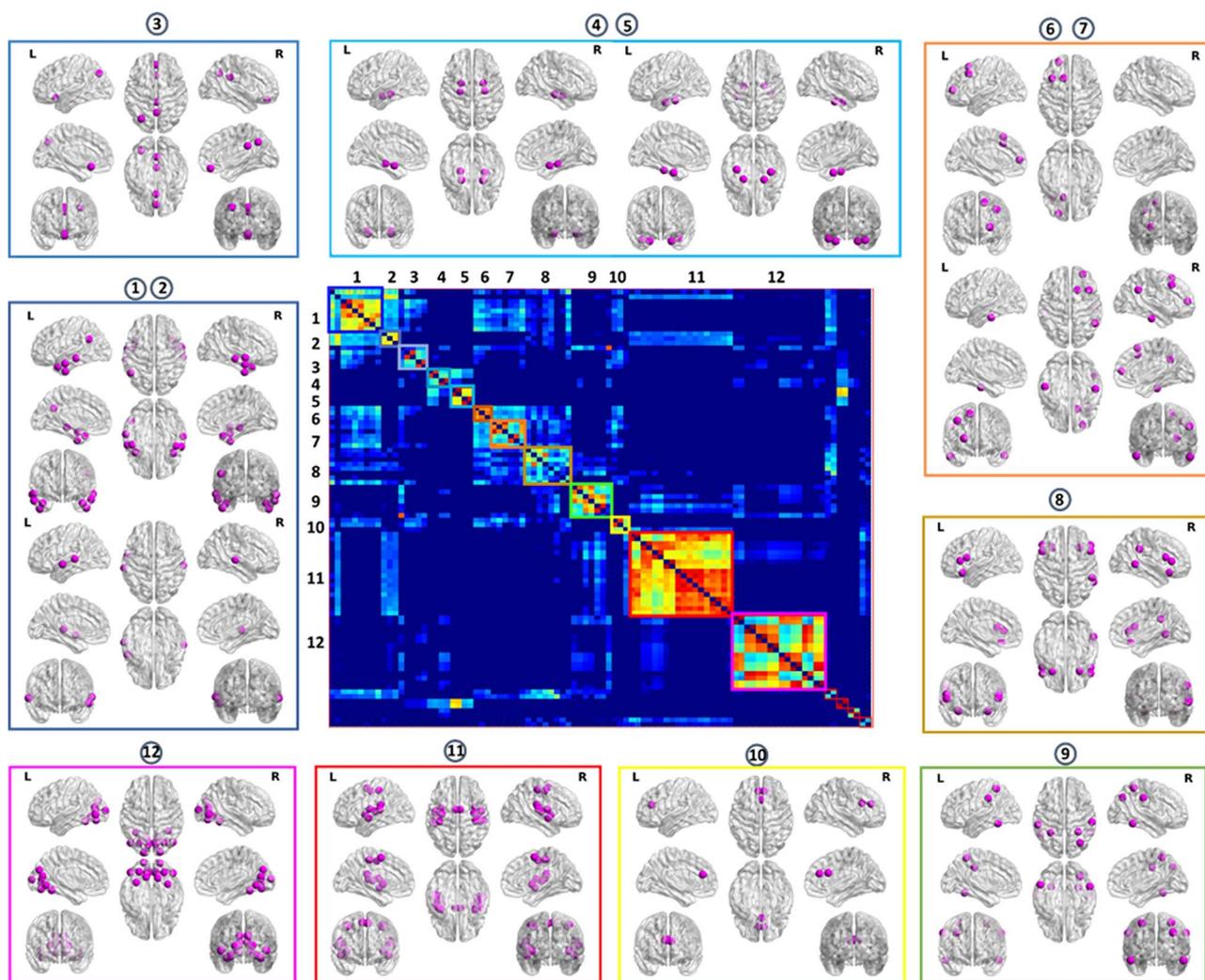


Fig. 3. Agreement matrix and functional communities in the representative partition for the CONTROL group at the third topological scale (Harvard-Oxford Atlas; 95 regions). Box colors denote putative functional labels (see Table 1).

that is not accessible when exclusively studying FC matrices (Bassett et al. 2015). In this context, two nodes consistently allocated to the same community are susceptible to present functional similarities.

The differences observed when comparing the agreement matrices of the two groups (DiffAM) are spatially organized and remain present across topological scales. Furthermore, a more detailed picture emerges when carrying permutation analysis and controlling for multiple comparisons.

Hypo-colocalized nodes in posttraumatic stress disorder

Concerning the coarser topological scale (~2 communities), we found a reduced colocalization between regions in the middle temporal, posterior-anterior medial, and frontal cortices in the PTSD group (Fig. 4 top left, and Supplementary Fig. 7). When increasing the number of communities (~12 communities), the hypo-colocalized nodes were mainly within and between communities in association cortices containing nodes of the DMN (blue communities) and FPCN (orange communities). Importantly, we show that the decreased co-localization of these regions remains present across different topological resolutions. Our results are in line with findings in adult and adolescent PTSD showing a decreased functional interaction between regions belonging to the DMN (Miller et al. 2017; Akiki et al. 2018; Viard et al. 2019; Sheynin

et al. 2020; Bao et al. 2021). Our results also align with those of Breukelaar et al. (2021), where using a whole-brain approach in a cohort of adult PTSD, the authors found a hypo-connected subnetwork including regions from the DMN, control, and limbic (hippocampal complex + amygdala) communities in the PTSD group.

When running permutation analysis and controlling for multiple comparisons, we found the most implicated regions are in the anterior medial prefrontal cortex (amPFC) and the lateral-temporal cortex (black stars in Fig. 4 left and Supplementary Fig. 4). The amPFC is considered a functional bridge between the DMNmtl and the DMNsub3, two subsystems composing the DMN (Andrews-Hanna et al. 2010; Christoff et al. 2016). Therefore, the hypo-colocalization found here, specifically concerning the anterior part of the DMN, could be related to a lack of global functional integration between DMN subsystems in adolescent PTSD.

Interestingly, results from Akiki et al. 2018, obtained using a different methodological approach compared to the one presented here, show that the anterior part of the DMN is disconnected from the rest of the DMN in adult PTSD. Complementary to the investigation of Akiki and colleagues, we found similar results using a whole-cortex and multiscale approach where the DMN connectivity pattern is integrated into the whole-cortex network

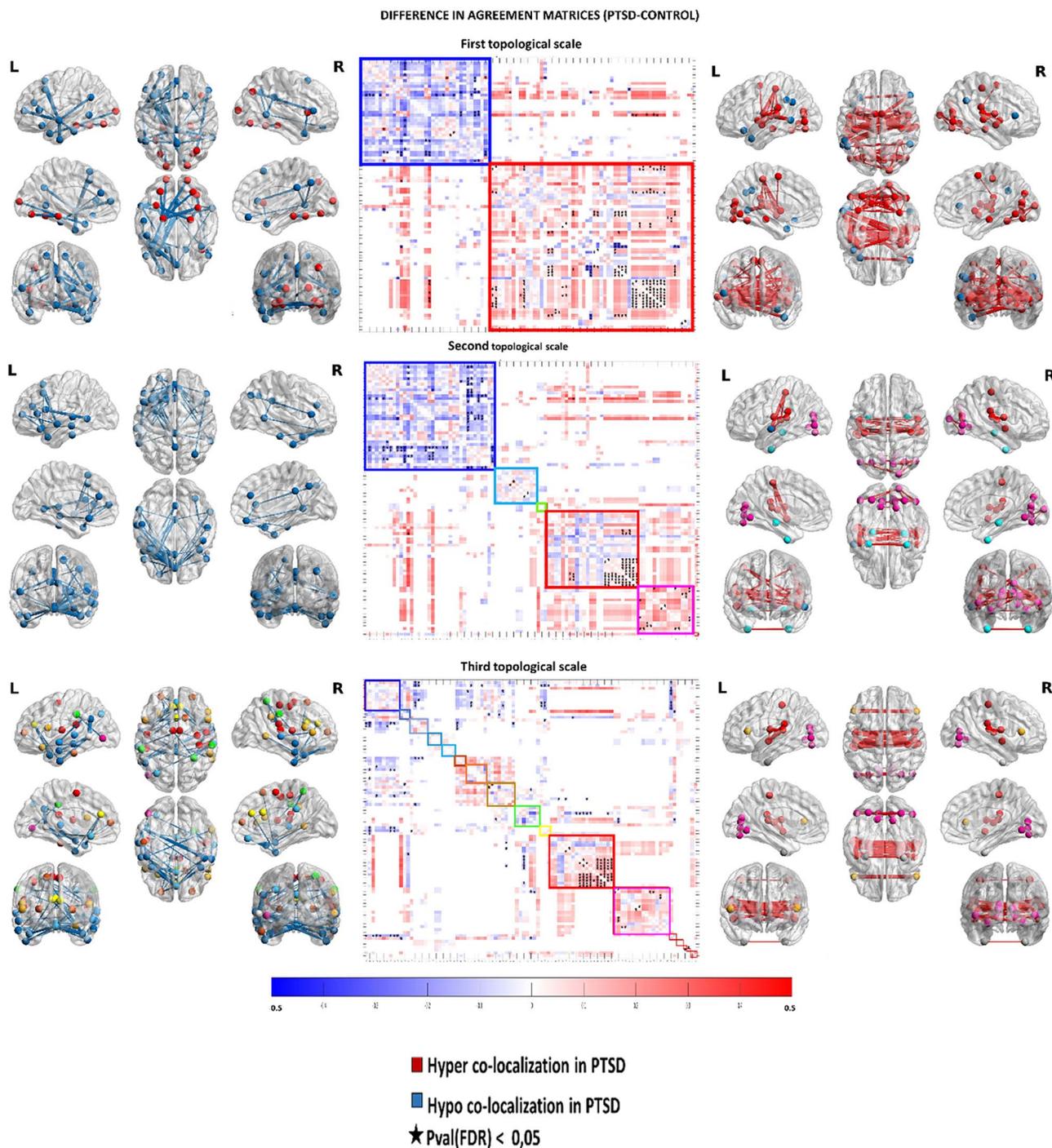


Fig. 4. The difference in agreement matrices (PTSD—Control) (DiffAM) in the first (top), second (intermediate), and third (bottom) topological scales (Harvard—Oxford Atlas). Entries >0 (red) correspond to pairs of nodes that are more co-localized (hyper-colocalized) in the PTSD group compared to the control group. Entries <0 (blue) correspond to hypo-colocalized nodes in the PTSD group compared to the control group, and entries equal to zero (white) denote no difference between groups. Entries with bright colors in the DiffAMs correspond to the remaining differences after permutations. Black stars in matrices and depicted edges in brain plots correspond to significant results after correction for multiple comparisons. For illustrative purposes, we plot the matrices according to the representative partition of the control group.

and analyzed across different topological scales. Together, these findings point to a particular relevance of the anterior DMN in PTSD independent of the developmental stage of patients. Our findings are also in line with previous results obtained using graph theory measures showing a decreased integration in regions belonging to the DMN (Akiki et al. 2018; Sheynin et al. 2020).

Finally, the decreased co-localization of DMN regions (maximally distant from sensory regions) (Margulies et al. 2016), whose

activity is mainly driven by endogenous dynamics and participates in the replay of past experiences (Kaefer et al. 2022), could be related to negative cognition and intrusive symptoms in PTSD patients (Akiki et al. 2018).

Hyper-colocalized nodes in posttraumatic stress disorder

Across topological scales, we also found an increased co-localization of regions in occipital and pericentral cortices (red

Table 1. Labels of communities in the third topological scale for the control group (see Fig. 3). “r/l” at the end of the region’s name denotes bilateral regions. R for right, l for left. Singletons’ communities (i.e. a one-node or bilateral node community) are not presented.

Control Group		
Community	Brain Regions	Putative Functional Label
1 (dark blue)	TPr/l	Default Network lateral (DNsub3)
	aSTGr	
	aMTGr/l	
	pMTGr/l	
	aITGr/l	
2 (dark blue)	AGl	Dn sub3
	aSTGl	
3 (blue)	pSTGr/l	Default Network core (Dnc)
	sLOC l	
	MedFC	
	SubCa	
	PC	
4 (light blue)	Precu	Default Network MTL
	aPaHC r/l	
	pTFusr/l	
5 (light blue)	Hippo r/l	Default Network MTL
	Amygdr/l	
6 (orange)	FPr	FPCN A
	SFGr	
	MidFGGr	
	pITGr/l	
7 (orange)	AGr	FPCN A
	FPl	
	SFGl	
8 (orange)	MidFGl	FPCN B
	IFGtr/l	
	IFGor/l	
	toMTGr	
	pSMGr	
9 (green)	FORb r/l	Dorsal attention network
	toITGr/l	
	SPLr/l	
	aSMGr/l	
10 (yellow)	sLOCr	Salience Network
	AC	
	PaCiGr/l	
11 (red)	ICr/l	Somatomotor network
	PreCCGr/l	
	PostCr/l	
	SMAr/l	
	COr/l	
	POr/l	
	PPr/l	
	HGr/l	
	PTr/l	
	iLOCr/l	
12 (pink)	ICCr/l	Visual Network
	Cunea r/l	
	LGr/l	
	TOFusr/l	
	OFusGr/l	
	SCCr/l	
	Opr/l	

and pink communities) (Fig. 4, right). When controlling for spurious results using permutations and multiple comparisons, we found a set of hyper-colocalized regions belonging to occipital (visual), auditory, and motor cortices. These results mirror recent findings showing a hyper-connected somatomotor network in adults with PTSD while recalling morally injurious memories

Table 2. Labels of communities in the third topological scale for the PTSD group (see Fig. 3). “r/l” at the end of the region’s name denotes bilateral regions. R for right, l for left. Singletons’ communities (i.e. a one-node or bilateral node community) are not presented.

PTSD Group		
Community	Brain Regions	Putative Functional Label
1 (dark blue)	TPr/l	Default Network lateral (DNsub3)
	pSTGl	
	aMTGr/l	
	pMTGr/l	
	aITGr/l	
2 (blue)	AGl	Default Network core (Dnc)
	MedFC	
	SubCa	
3 (light blue)	PC	Default Network MTL
	Precu	
	aPaHC r/l	
4 (light blue)	pTFusr/l	Default Network MTL
	pPaHCr/l	
5 (orange)	Hippo r/l	FPCN A
	Amygdr/l	
	FPr/l	
	SFGr/l	
6 (orange)	MidFGGr/l	FPCN B
	pITGr/l	
	AGr	
	IFGtr/l	
	IFGor/l	
7 (green)	toMTGr/l	Dorsal attention network
	pSMGr/l	
	FORb r/l	
	toITGr/l	
	SPLr/l	
8 (yellow)	aSMGl	Salience Network
	sLOCr/l	
	AC	
	PaCiGr/l	
9 (red)	ICr/l	Somatomotor network
	PreCCGr/l	
	aSTGr/l	
	PostCr/l	
	aSMGr	
	SMAr/l	
	COr/l	
	POr/l	
	PPr/l	
	HGr/l	
10 (pink)	PTr/l	Visual Network
	iLOCr/l	
	ICCr/l	
	Cunea r/l	
	LGr/l	
	TOFusr/l	
	OFusGr/l	
	SCCr/l	
Opr/l		

compared to controls who had experienced a potentially morally injurious event (Kearney et al. 2023). Because of the small sample size in the present work, it is unwise to speculate about the potential underlying psychopathological implication of our results. However, in line with Kearney et al. (2023) and other investigations presenting the relevance of the somatomotor cortices in PTSD (Bao et al. 2021), we note that paying more attention to the overlooked sensorimotor regions in PTSD brain

investigations could be important to further clarify the brain specificities in the deleterious consequences of experiencing traumatic events.

In a study evaluating whole brain (connectome-wide association) resting state FC in combat veterans, Misaki et al. (2018) found a decreased connectivity between the parahippocampal gyrus and occipital areas. In addition, Breukelaar et al. (2021) found regions from visual and somatomotor cortices belonging to a hypo-connected network, which contradicts our results. In this later study, the participants were aged between 19 and 63 with a time since trauma of 0.75 to 51 years (~20 years on average).

In the present study, the participants were younger with a more recent trauma, which could explain the still predominant involvement of the unimodal cortices implicated in the implementation of a defensive peripersonal space (defense zone with rapid detection of a potential threat) characterized by automatic protective actions (Rabellino et al. 2020). Along the same line, within the framework of large-scale gradients in the cortical organization (Huntenburg et al. 2018), the exacerbated coupling in sensory regions—whose activity is mainly driven by environmental inputs—could be related to hypervigilance-related symptoms in PTSD.

Compared to other investigations studying the whole-brain functional organization in PTSD, our results present specificities that could be linked to adolescent PTSD compared to adult PTSD. The increased co-localization in sensorimotor regions could be a particularity of adolescent trauma, with an increased propensity to defensive strategies compared to adulthood. An alternative explanation accounting for these results would be linked to the proximity of the traumatic event rather than the age of trauma. Future longitudinal studies and direct comparisons between adult and adolescent PTSD are necessary to disentangle these two possibilities.

New avenues of research on posttraumatic stress disorder

The results presented here open up an intriguing line of research to understand the underlying reasons for the exacerbated co-localization in sensory regions and the decreased co-localization in association regions. The unimodal-transmodal canonical organization in the functional macroscale brain architecture has been related to brain region characteristics, including principally (i) the diversity in their time series, with sensory regions showing an increased pattern of dynamic diversity compared to association regions (Shafiei et al. 2020); (ii) the coupling between the structural and FC, with sensory regions presenting an increased coupling strength between structure and function, compared to association cortices (Preti and Van De Ville 2019; Vázquez-Rodríguez et al. 2019); (iii) the temporal receptive windows (the time window within which a new stimulus will affect previously presented information), with sensory regions presenting a higher temporal integration (Hasson et al. 2015; Chien and Honey 2020); and (iv) the sensitivity of excitation-inhibition imbalance, with increased sensitivity in association regions (Yang et al. 2016).

Although this is not an exhaustive list accounting for the unimodal-transmodal organization, our results suggest that one or more of these characteristics could be at risk in patients with PTSD. Similar alterations to this organization have been shown in other clinical conditions, such as schizophrenia (Yang et al. 2016) and autism spectrum disorder (Watanabe et al. 2019), pointing out an atypical excitatory/inhibitory balance in association cortices and shorter neural timescales in sensory cortices, respectively.

Thus, investigating the cortical gradient in PTSD could be an interesting avenue to understanding the functional brain organization in this pathology and its relation to clinical symptoms.

Importantly, this type of analysis could take advantage of an essential feature of the MSCD that we did not use here because of our small sample, namely the subject-specific community partitions. The possibility of obtaining reliable subject-specific partitions sharing community labels (e.g. community 1 in subject 1 is community 1 in subject 2) is a powerful tool that could be used in other investigations. For instance, by mixing the MSCD with the approach of Lobo and colleagues (Lebois et al. 2021), in which they created subject-specific brain regions (versus classical group-based brain regions, e.g. Harvard–Oxford Atlas), it would be possible to gain an unprecedented detail in subject-specific brain organization easily comparable across subjects, and groups.

Limitations

The main limitations of this work are the small sample size in our experiment, the absence of a control group of exposed subjects to a traumatic event without PTSD and the PTSD group mainly consisting of female subjects, which limits the generalizability of the findings and precludes a reliable conclusion concerning whether our results reflect PTSD rather than trauma-related specificities. Therefore, the analysis presented here requires to be replicated with a different and bigger cohort, including a control group of trauma-exposed subjects without PTSD. Furthermore, because of the small sample size, we did not differentiate PTSD subtypes, which have been shown to present important specificities in their functional organization, for instance, in dissociative PTSD (Shaw et al. 2023). The differentiation between these expressions of PTSD requires attention in future investigations seeking to characterize the brain functional specificities in PTSD subtypes. Because the MSCD method allows the inclusion of different subjects and groups in a single mathematical structure, it could be used to further understand the specificities of different PTSD subtypes and compared to the consequences of trauma experience without PTSD.

Finally, from a methodological stance, MSCD relies on a specific definition of community, namely a set of nodes more connected to each other than with other nodes in the network. This type of modular organization is called assortative. However, although an assortative structure is well suited to host simultaneously segregated communities and efficient communication, there are different possible modular organizations (e.g. core-periphery, disassortative) that are not studied when using the MSCD (Fortunato and Hric 2016; Betzel et al. 2018; Hanteer and Magnani 2020; Murphy et al. 2020).

Although we recognize these issues, our investigation presents interesting results in an understudied group of clinical participants. Moreover, we highlight the importance in clinical neuroscience of paying attention to unexplored brain regions associated with sensorimotor processes and present a method to compare whole-brain functional data from different populations straightforwardly.

Conclusion

In this work, we were interested in detailing the functional brain organization of adolescent PTSD using a whole cortex and multiscale topological approach. To do so, we built on the network neuroscience framework, specifically in multisubject community analysis. Our results open up an interesting perspective concerning a possible alteration in the large-scale cortical organization in

PTSD. Testing for the possible explanations underlying the exacerbated coupling in sensory regions and the decreased coupling in association regions could be the object of future investigations. This work shows the utility of the MSCD method to study brain specificities in clinical conditions and invites its application in larger cohorts to challenge the obtained results.

Acknowledgments

This study was supported by the University Hospital of Caen, the Caen School District and the Mutuelle Générale de l'Éducation Nationale (insurance company) and the Observatoire B2V des mémoires. We would like to thank Gina Joue and Cecile Bordier for their helpful feedback during the analysis implementation and all the persons involved in the data acquisition. We are also thankful to the adolescents and institutions participating in our research.

Author contributions

David Corredor (Conceptualization, Methodology, Formal Analysis, Software, Writing—original draft), Shailendra Segobin (Conceptualization, Writing—review), Thomas Hinault (Writing—review), Francis Eustache (Funding acquisition, Writing—review), Jacques Dayan (Writing—review), Bérengère Guillery-Girard (Conceptualization, Supervision, Funding acquisition, Writing—review & editing), Mikaël Naveau (Conceptualization, Supervision, Writing—review & editing).

Supplementary material

Supplementary material is available at *Cerebral Cortex* online.

Conflict of interest statement: The authors declare no conflicting interests.

Data and code availability

Subject-level adjacency matrices and code are available at <http://dx.doi.org/10.5281/zenodo.8164459>.

References

Akiki TJ, Averill CL, Wrocklage KM, Scott JC, Averill LA, Schweinsburg B, Alexander-Bloch A, Martini B, Southwick SM, Krystal JH, et al. Default mode network abnormalities in posttraumatic stress disorder: A novel network-restricted topology approach. *NeuroImage*. 2018;176:489–498. <https://doi.org/10.1016/j.neuroimage.2018.05.005>.

Alexander-Bloch A, Lambiotte R, Roberts B, Giedd J, Gogtay N, Bullmore E. The discovery of population differences in network community structure: New methods and applications to brain functional networks in schizophrenia. *NeuroImage*. 2012;59(4):3889–3900. <https://doi.org/10.1016/j.neuroimage.2011.11.035>.

Andrews-Hanna JR, Reidler JS, Sepulcre J, Poulin R, Buckner RL. Functional Fractionation of the Brain's Default Network. *Neuron*. 2010;65(4):550–562. <https://doi.org/10.1016/j.neuron.2010.02.005>.

Artime O, Benigni B, Bertagnolli G, d'Andrea V, Gallotti R, Ghavasiéh A, De Domenico M. *Multilayer network science: from cells to societies*. Cambridge University Press; 2022

Avena-Koenigsberger A, Misić B, Sporns O. Communication dynamics in complex brain networks. *Nat Rev Neurosci*. 2017;19(1):17–33. <https://doi.org/10.1038/nrn.2017.149>. PMID: 29238085.

Bao W, Gao Y, Cao L, Li H, Liu J, Liang K, Hu X, Zhang L, Hu X, Gong Q, et al. Alterations in large-scale functional networks in adult posttraumatic stress disorder: A systematic review and meta-analysis of resting-state functional connectivity studies. *Neurosci Biobehav Rev*. 2021;131:1027–1036. <https://doi.org/10.1016/j.neubiorev.2021.10.017>.

Bassett DS, Porter MA, Wymbs NF, Grafton ST, Carlson JM, Mucha PJ. Robust detection of dynamic community structure in networks. *Chaos: An Interdisciplinary Journal of Nonlinear Science*. 2013;23(1):013142. <https://doi.org/10.1063/1.4790830>.

Bassett DS, Yang M, Wymbs NF, Grafton ST. Learning-induced autonomy of sensorimotor systems. *Nat Neurosci*. 2015;18(5):744–751. <https://doi.org/10.1038/nn.3993>.

Bazzi M, Porter MA, Williams S, McDonald M, Fenn DJ, Howison SD. Community Detection in Temporal Multilayer Networks, with an Application to Correlation Networks. *Multiscale Modeling & Simulation*. 2016;14(1):1–41. <https://doi.org/10.1137/15M1009615>.

Betzell RF, Medaglia JD, Bassett DS. Diversity of meso-scale architecture in human and non-human connectomes. *Nat Commun*. 2018;9(1):346. <https://doi.org/10.1038/s41467-017-02681-z>.

Betzell RF. Community detection in network neuroscience. *ArXiv:201106723 [q-Bio]*. 2020. <http://arxiv.org/abs/2011.06723>.

Betzell RF, Bertolero MA, Gordon EM, Gratton C, Dosenbach NUF, Bassett DS. The community structure of functional brain networks exhibits scale-specific patterns of inter- and intra-subject variability. *NeuroImage*. 2019;202:115990. <https://doi.org/10.1016/j.neuroimage.2019.07.003>.

Bruckelaar IA, Bryant RA, Korgaonkar MS. The functional connectome in posttraumatic stress disorder. *Neurobiology of Stress*. 2021;14:100321. <https://doi.org/10.1016/j.ynstr.2021.100321>.

Chien H-YS, Honey CJ. Constructing and Forgetting Temporal Context in the Human Cerebral Cortex. *Neuron*. 2020;106(4):675–686.e11. <https://doi.org/10.1016/j.neuron.2020.02.013>.

Christoff K, Irving ZC, Fox KCR, Spreng RN, Andrews-Hanna JR. Mind-wandering as spontaneous thought: a dynamic framework. *Nat Rev Neurosci*. 2016;17(11):718–731. <https://doi.org/10.1038/nrn.2016.113>.

Cisler JM, Herringa RJ. Posttraumatic Stress Disorder and the Developing Adolescent Brain. *Biol Psychiatry*. 2021;89(2):144–151. <https://doi.org/10.1016/j.biopsych.2020.06.001>.

Fortunato S, Hric D. Community detection in networks: A user guide. *Phys Rep*. 2016;659:1–44. <https://doi.org/10.1016/j.physrep.2016.09.002>.

Hanteer O, Magnani M. Unspoken Assumptions in Multilayer Modularity Maximization. *Sci Rep*. 2020;10(1):11053. <https://doi.org/10.1038/s41598-020-66956-0>.

Hasson U, Chen J, Honey CJ. Hierarchical process memory: memory as an integral component of information processing. *Trends Cogn Sci*. 2015;19(6):304–313. <https://doi.org/10.1016/j.tics.2015.04.006>.

Huntenburg JM, Bazin P-L, Margulies DS. Large-Scale Gradients in Human Cortical Organization. *Trends Cogn Sci*. 2018;22(1):21–31. <https://doi.org/10.1016/j.tics.2017.11.002>.

Kaefer K, Stella F, McNaughton BL, Battaglia FP. Replay, the default mode network and the cascaded memory systems model. *Nat Rev Neurosci*. 2022;23(10):628–640. <https://doi.org/10.1038/s41583-022-00620-6>.

Kearney BE, Terpou BA, Densmore M, Shaw SB, Théberge J, Jetly R, Lanius RA. How the body remembers: examining the default mode and sensorimotor networks during moral injury autobiographical memory retrieval in PTSD. *NeuroImage: clinical*. 2023;38:103426. <https://doi.org/10.1016/j.nicl.2023.103426>.

Lebois LAM, Li M, Baker JT, Wolff JD, Wang D, Lambros AM, Grinspoon E, Winternitz S, Ren J, Gönenç A, et al. Large-Scale Functional

- Brain Network Architecture Changes Associated With Trauma-Related Dissociation. *Am J Psychiatry*. 2021;178(2):165–173. <https://doi.org/10.1176/appi.ajp.2020.19060647>.
- Leibenluft E, Barch DM. Adolescent Brain Development and Psychopathology: Introduction to the Special Issue. *Biol Psychiatry*. 2021;89(2):93–95. <https://doi.org/10.1016/j.biopsych.2020.11.002>.
- Margulies DS, Ghosh SS, Goulas A, Falkiewicz M, Huntenburg JM, Langs G, Bezgin G, Eickhoff SB, Castellanos FX, Petrides M, et al. Situating the default-mode network along a principal gradient of macroscale cortical organization. *Proc Natl Acad Sci*. 2016;113(44):12574–12579. <https://doi.org/10.1073/pnas.1608282113>.
- Marshall AD. Developmental Timing of Trauma Exposure Relative to Puberty and the Nature of Psychopathology Among Adolescent Girls. *J Am Acad Child Adolesc Psychiatry*. 2016;55(1):25–32.e1. <https://doi.org/10.1016/j.jaac.2015.10.004>.
- McLaughlin KA, Koenen KC, Hill ED, Petukhova M, Sampson NA, Zaslavsky AM, Kessler RC. Trauma exposure and posttraumatic stress disorder in a national sample of adolescents. *J Am Acad Child Adolesc Psychiatry*. 2013;52(8):815–830.e14. <https://doi.org/10.1016/j.jaac.2013.05.011>.
- Mesulam MM. From sensation to cognition. *Brain J Neurol*. 1998;121(Pt 6):1013–1052. <https://doi.org/10.1093/brain/121.6.1013>.
- Miller DR, Hayes SM, Hayes JP, Spielberg JM, Lafleche G, Verfaellie M. Default Mode Network Subsystems Are Differentially Disrupted in Posttraumatic Stress Disorder. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. 2017;2(4):363–371. <https://doi.org/10.1016/j.bpsc.2016.12.006>.
- Misaki M, Phillips R, Zotev V, Wong C-K, Wurfel BE, Krueger F, Feldner M, Bodurka J. Connectome-wide investigation of altered resting-state functional connectivity in war veterans with and without posttraumatic stress disorder. *NeuroImage: Clinical*. 2018;17:285–296. <https://doi.org/10.1016/j.nicl.2017.10.032>.
- Mucha PJ, Richardson T, Macon K, Porter MA, Onnela J-P. Community Structure in Time-Dependent, Multiscale, and Multiplex Networks. *Science*. 2010;328(5980):876–878. <https://doi.org/10.1126/science.1184819>.
- Murphy AC, Bertolero MA, Papadopoulos L, Lydon-Staley DM, Bassett DS. Multimodal network dynamics underpinning working memory. *Nature. Communications*. 2020;11(1):3035. <https://doi.org/10.1038/s41467-020-15541-0>.
- Pitman RK, Rasmusson AM, Koenen KC, Shin LM, Orr SP, Gilbertson MW, Milad MR, Liberzon I. Biological studies of posttraumatic stress disorder. *Nat Rev Neurosci*. 2012;13(11):769–787. <https://doi.org/10.1038/nrn3339>.
- Preti MG, Van De Ville D. Decoupling of brain function from structure reveals regional behavioral specialization in humans. *Nat Commun*. 2019;10:4747. <https://doi.org/10.1038/s41467-019-12765-7>.
- Puxeddu MG, Faskowitz J, Betzel RF, Petti M, Astolfi L, Sporns O. The modular organization of brain cortical connectivity across the human lifespan. *NeuroImage*. 2020;218:116974. <https://doi.org/10.1016/j.neuroimage.2020.116974>.
- Rabellino D, Frewen PA, McKinnon MC, Lanius RA. Peripersonal Space and Bodily Self-Consciousness: Implications for Psychological Trauma-Related Disorders. *Front Neurosci*. 2020;14:586605. <https://doi.org/10.3389/fnins.2020.586605>.
- Ross MC, Cisler JM. Altered large-scale functional brain organization in posttraumatic stress disorder: A comprehensive review of univariate and network-level neurocircuitry models of PTSD. *NeuroImage: Clinical*. 2020;27:102319. <https://doi.org/10.1016/j.nicl.2020.102319>.
- Shafiei G, Markello RD, Vos de Wael R, Bernhardt BC, Fulcher BD, Misic B. Topographic gradients of intrinsic dynamics across neocortex. *elife*. 2020;9:e62116. <https://doi.org/10.7554/eLife.62116>.
- Shaw SB, Terpou BA, Densmore M, Théberge J, Frewen P, McKinnon MC, Lanius RA. Large-scale functional hyperconnectivity patterns in trauma-related dissociation: an rs-fMRI study of PTSD and its dissociative subtype. *Nature Mental Health*. 2023;1(10):711–721.
- Sheynin J, Duval ER, Lokshina Y, Scott JC, Angstadt M, Kessler D, Zhang L, Gur RE, Gur RC, Liberzon I. Altered resting-state functional connectivity in adolescents is associated with PTSD symptoms and trauma exposure. *NeuroImage: Clinical*. 2020;26:102215. <https://doi.org/10.1016/j.nicl.2020.102215>.
- Shin LM, Rauch SL, Pitman RK. Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. *Ann N Y Acad Sci*. 2006;1071:67–79. <https://doi.org/10.1196/annals.1364.007>.
- Sporns O. *Networks of the brain*. MIT Press; 2011.
- Thiebaut de Schotten M, Forkel SJ. The emergent properties of the connected brain. *Science*. 2022;378(6619):505–510. <https://doi.org/10.1126/science.abq2591>.
- Uddin LQ, Yeo BTT, Spreng RN. Towards a Universal Taxonomy of Macro-scale Functional Human Brain Networks. *Brain Topogr*. 2019;32(6):926–942. <https://doi.org/10.1007/s10548-019-00744-6>.
- Uddin L, Betzel R, Cohen J, Damoiseaux J, De Brigard F, Eickhoff S, Fornito A, Gratton C, Gordon E, Laird A, Larson-Prior L, McIntosh A, Nickerson L, Pessoa L, Pinho A, Poldrack R, Razi A, Sadaghiani S, Shine J, & Spreng R N. (2022). *Controversies and current progress on large-scale brain network nomenclature from OHBM WHAT-NET: Workgroup for HARmonized Taxonomy of NETworks*. <https://doi.org/10.31219/osf.io/25za6>
- Vaiana M, Muldoon SF. Multilayer Brain Networks. *Journal of Nonlinear Science*. 2020;30(5):2147–2169. <https://doi.org/10.1007/s00332-017-9436-8>.
- Vázquez-Rodríguez B, Suárez LE, Markello RD, Shafiei G, Paquola C, Hagmann P, van den Heuvel MP, Bernhardt BC, Spreng RN, Misic B. Gradients of structure–function tethering across neocortex. *Proc Natl Acad Sci*. 2019;116(42):21219–21227. <https://doi.org/10.1073/pnas.1903403116>.
- Viard A, Mutlu J, Chanraud S, Guenolé F, Egler P-J, Gérardin P, Baleyte J-M, Dayan J, Eustache F, Guillery-Girard B. Altered default mode network connectivity in adolescents with posttraumatic stress disorder. *NeuroImage: Clinical*. 2019;22:101731. <https://doi.org/10.1016/j.nicl.2019.101731>.
- Watanabe T, Rees G, Masuda N. Atypical intrinsic neural timescale in autism. *elife*. 2019;8:e42256. <https://doi.org/10.7554/eLife.42256>.
- Yang GJ, Murray JD, Wang X-J, Glahn DC, Pearlson GD, Repovs G, Krystal JH, Anticevic A. Functional hierarchy underlies preferential connectivity disturbances in schizophrenia. *Proc Natl Acad Sci*. 2016;113(2):E219–E228. <https://doi.org/10.1073/pnas.1508436113>.
- Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, Roffman JL, Smoller JW, Zöllei L, Polimeni JR, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol*. 2011;106(3):1125–1165. <https://doi.org/10.1152/jn.00338.2011>.