EJN European Journal of Neuroscience

FENS Federation of European Neuroscience Societies

European Journal of Neuroscience, Vol. 45, pp. 1224–1229, 2017 doi:10.1111/ejn.13544

NEUROSYSTEMS

Functional connectivity in amygdalar-sensory/(pre)motor networks at rest: new evidence from the Human Connectome Project

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Keywords: amygdala, limbic circuits, premotor cortex, resting-state fMRI, sensory-motor cortex

Edited by John Foxe
Received 26 July 2016, revised 7 February 2017, accepted 10 February 2017

Abstract

The word 'e-motion' derives from the Latin word 'ex-moveo' which literally means 'moving away from something/somebody'. Emotions are thus fundamental to prime action and goal-directed behavior with obvious implications for individual's survival. However, the brain mechanisms underlying the interactions between emotional and motor cortical systems remain poorly understood. A recent diffusion tensor imaging study in humans has reported the existence of direct anatomical connections between the amygdala and sensory/(pre)motor cortices, corroborating an initial observation in animal research. Nevertheless, the functional significance of these amygdala-sensory/(pre)motor pathways remain uncertain. More specifically, it is currently unclear whether a distinct amygdala-sensory/(pre)motor circuit can be identified with resting-state functional magnetic resonance imaging (rs-fMRI). This is a key issue, as rs-fMRI offers an opportunity to simultaneously examine distinct neural circuits that underpin different cognitive, emotional and motor functions, while minimizing task-related performance confounds. We therefore tested the hypothesis that the amygdala and sensory/(pre)motor cortices could be identified as part of the same resting-state functional connectivity network. To this end, we examined independent component analysis results in a very large rs-fMRI data-set drawn from the Human Connectome Project (n = 820 participants, mean age: 28.5 years). To our knowledge, we report for the first time the existence of a distinct amygdala-sensory/(pre)motor functional network at rest. rs-fMRI studies are now warranted to examine potential abnormalities in this circuit in psychiatric and neurological diseases that may be associated with alterations in the amygdala-sensory/(pre)motor pathways (e.g. conversion disorders, impulse control disorders, amyotrophic lateral sclerosis and multiple sclerosis).

Introduction

The English word 'e-motion' originates from the Latin word 'ex-moveo' which literally means 'moving away from somebody/something'. Hence, a fundamental role of emotions is to promote movement and prime goal-directed behavior (Damasio, 2001). The tight link between emotions and action control may also have ancient evolutionary roots as animals/individuals need to quickly adjust their behavior to environmental stimuli with rapidly changing affective value (i.e. threats vs. rewards). This implies that fast and direct interactions between emotional and sensory-motor cortical systems may occur to mediate such adaptive behaviors.

Consistent with this hypothesis, data from animal research have provided evidence of a direct link between the amygdala, a key emotional sub-cortical area and a number of sensory-motor cortical regions critically involved in sensory-motor control and action planning. In particular, anterograde and retrograde studies in monkeys, rats and cats (which assessed the axonal projections from and to specific brain regions) have found that the supplementary motor area (SMA) (Jurgens, 1984), cingulate motor area (Ghashghaei *et al.*, 2007), lateral premotor cortex (Avendano *et al.*, 1983; Amaral & Price, 1984; Llamas *et al.*, 1985), primary motor cortex (Macchi *et al.*, 1978; Sripanidkulchai *et al.*, 1984), and primary somato-sensory cortex receive direct inputs from the amygdala (Sripanidkulchai *et al.*, 1984).

More recently, a diffusion tensor imaging (DTI) study in humans employed probabilistic tractography to demonstrate mono-synaptic connections between the amygdala and sensory-motor areas like the lateral and medial pre-central cortex, motor cingulate, primary motor cortex and post-central gyrus (Grezes *et al.*, 2014). Further analyses

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revealed that the dorsal amygdala, which serves as the main amygdalar output nucleus, was more strongly connected with the motor than non-motor cortices (i.e. the orbitofrontal cortex, OFC, fusiform gyrus, FG, and superior temporal gyrus, STG) (Grezes *et al.*, 2014). In contrast, the baso-lateral amygdalar complex, which in turn receives the majority of the inputs directed to the amygdala, showed greater structural connectivity with the OFC, FG, and STG relative to the motor cortices (Grezes *et al.*, 2014). Overall, these findings showed that different amygdala sub-nuclei may have distinct patterns of anatomical connectivity with various cortical regions, which is likely to have important functional consequences (Grezes *et al.*, 2014). In particular, the existence of direct connections between an output nucleus of the amygdala and a set of cortical areas involved in motor planning may represent a key mechanism by which the amygdala influences goal-directed behavior over and above its well-known effects on autonomic and stereotypical motor responses (as those mediated via the hypothalamus and brainstem) (Grezes *et al.*, 2014).

On the other hand, the presence of direct connections between the amygdala and sensory cortical regions may also represent the brain basis of 'embodied' emotions (Damasio, 1994, 2001). Consistently with this theory, a study in healthy volunteers has found that the sight of distorted finger postures in others was associated with increased activation in the right primary motor cortex, post-central somatosensory areas, and amygdala (Schurmann *et al.*, 2011). Likewise, the functional patterns of activation in the right somatosensory cortex are linked to distinct, and somato-topically organized, emotional categories as well as self-reported sensory experiences (Kragel & LaBar, 2016). Together, these data provide support to the model positing that emotional feelings may be 'embodied' via specific brain mechanisms, which may also explain why emotions are able to modulate subjective sensorial experiences.

However, the functional significance of the putatively direct anatomical pathways between the amygdala and (pre)motor/sensory cortices remain uncertain. In particular, it is unclear whether the existence of such mono-synaptic routes between the amygdala and (pre)motor/sensory cortical areas facilitates synchronous activity between these regions. To address this issue, one can use resting-state functional magnetic resonance imaging (rs-fMRI), which enables to simultaneously examine distinct neural networks underpinning different cognitive, emotional and sensory-motor functions, while minimizing task-related performance confounds. More specifically, rs-fMRI permits to study the coherence in the spontaneous fluctuations of the blood–oxygenation–level–dependent (BOLD) signal between inter-connected brain areas (Raichle, 2015). Hence, given the evidence for putative direct connections between the amygdala and sensory/(pre)motor cortices, it should be possible to identify a separate amygdala-sensory/(pre)motor network using rs-fMRI. Surprisingly, no study thus far has reported the existence of such a distinct amygdala-sensory/(pre)motor network, although a past rs-fMRI study in $n = 65$ participants found increased functional connectivity between the amygdala and pre-central gyrus within the context of a more extended circuit including other pre-frontal areas like the medial frontal gyrus (BA 11), superior frontal gyrus (BA 10), and anterior cingulate cortex (BA 32) (Roy *et al.*, 2009). All in all, the fact that no distinct amygdala-sensory/(pre) motor network at rest has clearly emerged in earlier studies may have depended on a number of factors including poor awareness of the importance of such circuit, reduced statistical power to detect it (e.g. due to small sample sizes), or the use of different analytical approaches across studies that may have obscured the presence of this network.

To overcome these limitations and test the hypothesis that a specific circuit including the amygdala and sensory/(pre)motor regions can be identified with rs-fMRI, we employed a large and homogeneous sample of healthy and young participants ($n = 820$, age-range: 22–37 years, four scans per subject, 1200 volumes per scan). This very rich rs-fMRI data-base was drawn from a public repository of structural and functional neuroimaging measures, which were made available via the Human Connectome Project (HCP) (http://www.humanconnectome.org/), a world-wide collaborative project that aims at exploring the basic aspects of the human brain structure and function (Van Essen *et al.*, 2013).

Methods

Participants

rs-fMRI data were acquired in 820 participants at 3 Tesla in four runs of approximately 15 min each, two runs in one session and two in another session, with eyes open with relaxed fixation on a projected bright cross-hair on a dark background (and presented in a darkened room). All participants were young and healthy adults (age-range: 22–36 years) with no medical or neuro-psychiatric disorders including hypertension, alcohol abuse, anxiety or depressive disorders and behavioral problems during childhood (i.e. conduct disorder) (see Table 1 for further details on demographics and clinical variables).

Magnetic resonance imaging (MRI) scanning

Within each session, oblique axial acquisitions alternated between phase encoding in a right-to-left (RL) direction in one run and phase encoding in a left-to-right (LR) direction in the other run. Acquisitions parameters were as follows: Gradient-echo echo-planar

TABLE 1. Demographic and clinical data in the sample ($n = 820$) drawn from the Human Connectome Project public repository data-set

		1st Quartile	Median	3rd Quartile
Age (years)		26	29	32
Handedness		60	80	90
Height (cm)		163	170	178
Weight (Kg)		64	75	89
Body Mass Index		22.7	25.42	29.26
Blood Pressure Systolic (mmHg)		114	122	132
Blood Pressure Diastolic (mmHg)		70	76	83
Number of Conduct Disorder symptoms (during childhood)		0	0	1
Number of Panic Disorder symptoms		0	0	0
Number of Depressive symptoms		0	0	0
Total number of Drinks per week		0	2	6
Race	American Indian/ Alaskan natural			2
	Asian/Natural Hawaiian/Other Pacific			45
	Black or African Americans			131
	More than one			19
	Unknown or not reported			13
Ethnicity	White			610
	Hispanic/Latino			70
	Not Hispanic/Latino			742
	Unknown or Not Reported			8

imaging, TR = 720 ms, TE = 33.1 ms, flip angle = 52°, FOV = 208 × 180 mm, Matrix 104 × 90, Slice thickness = 2.0 mm; 72 slices; 2.0 mm isotropic voxels, Multiband factor = 8, Echo spacing = 0.58 ms, BW = 2290 Hz/Px). This resulted in a total of 4800 rs-fMRI volumes per subject, subdivided into four sessions of 1200 volumes each. Structural (T1-weighted) images as well as field maps were also acquired in order to aid data preprocessing. Further details about data acquisition and processing (summarized below) can be found in the HCP S900 Release reference manual, available at https://www.humanconnectome.org/.

Resting-state fMRI (rs-fMRI) data analysis

Each 15-min (1200 volume) run of each subject's rs-fMRI data was pre-processed using FSL according to Smith *et al.* (Jenkinson *et al.*, 2012; Smith *et al.*, 2013); it was minimally pre-processed according to the latest version (3.1) of the HCP minimal pre-processing pipeline, which is especially designed to capitalize on the high data quality offered by HCP (Glasser *et al.*, 2013). This included gradient distortion correction, motion correction using FLIRT (also part of FSL), TOPUP-based (also part of FSL) field map pre-processing using spin echo field map (specific for each scanning day), distortion correction and registration into standard space using a customized boundary-based-registration (BBR) algorithm, one-step spline resampling from the original EPI into MNI space including all transforms, intensity normalization and bias field removal. Artifacts were removed using ICA+FIX (Griffanti *et al.*, 2014; Salimi-Khorshidi *et al.*, 2014). This involves employing an automatic classifier to identify ICA components due to measurement noise, additional motion or physiological artifacts like cardiac pulsation and respiration. Each dataset was then temporally demeaned and had variance normalization applied according to Beckmann *et al.* (Beckmann & Smith, 2004). Group-PCA output was generated by MIGP (MELODIC's Incremental Group-PCA), a technique that approximates full temporal concatenation of all subjects' data, from all 820 subjects. This comprises the top 4500 weighted spatial eigenvectors from a group-averaged PCA (Smith *et al.*, 2014). The MIGP output was then fed into group-ICA using FSL's MELODIC tool (Hyvarinen, 1999; Beckmann & Smith, 2004), applying spatial-ICA at dimensionality 15. Spatial-ICA was applied in gray-ordinate space (which includes surface vertices plus subcortical grey matter voxels (Glasser *et al.*, 2013), designed by the HCP consortium specifically for storing and processing large amounts of voxel-wise functional and structural data more efficiently). Successively, the ICA maps were dual-regressed into each subjects' 3D data. This is a two-stage procedure which involves regressing the group-wise spatial-maps into each subject's 4D dataset to give a set of time-courses, followed by regressing those time-courses into the same 4D dataset to create a subject-specific set of spatial maps. Finally, the subject-wise coefficients (*betas*) resulting from dual regression were averaged across subjects in Montreal Neurological Institute (MNI) space. All resulting maps were thresholded at the 99th percentile and visually inspected, after which automatic anatomical localization of global cluster-wise maxima as well as local maxima within each cluster was performed using the Jülich Histological Atlas (Eickhoff *et al.*, 2005) and the Harvard-Oxford Cortical and subcortical atlases (Desikan *et al.*, 2006). In order to verify the robustness of our results (and particularly the consistency of the components of identified networks) against the pre-determined number of components, the above analysis was re-examined while imposing a dimensionality of 25 (instead of 15) independent components.

Results

Figure 1 shows the results of thresholding the 13th ICA component at the 99th percentile along with the anatomical interpretation/localization of clusters surviving the threshold procedure. Table 2 shows the results of anatomical localization of all topologically connected clusters in the 13th ICA component after thresholding. Upon visual inspection, the hypothesized functional amygdala-sensory/(pre) motor network was detected in the 13th component of the 15-components group ICA analysis (Fig. 1). Of note, this network consistently contained the bilateral dorsal amygdala and SMA/pre-SMA when using 15-components group ICA analysis as well as the analysis with higher ICA-dimensionality (25 components), although the primary motor cortex was not present in the 25-components ICA and the sensory cortices were only found in the 15-components analyses (see Table S1).

Furthermore, we were able to confirm that the remaining ICA components (i.e. all components from the 1st to 15th apart from the 13th) contained a number of well-known motor, visual, cognitive and emotional networks that have been previously identified in past resting-state studies (e.g. the default-mode network, the fronto-parietal-cerebellar attentional networks, the motor-sensory networks, the visual networks, the salience network, etc.) (Raichle, 2015) (see Table S2).

Discussion

The current data support the existence of a distinct amygdala-sensory/(pre)-motor circuit at rest in a homogeneous and large sample of n = 820 participants drawn from the Human Connectome Project public repository (Van Essen *et al.*, 2013). Of note, the finding of this amygdala-sensory/(pre) motor network remained relatively consistent when varying the dimensionality of the main independent component analysis (ICA), that is, the number of components chosen to separate the correlations in the BOLD signal across regions into non-overlapping spatial and time components. The ability to identify such a distinct amygdala-sensory/(pre)-motor circuit at rest offers the possibility to assess the function of an important limbic-sensory/motor network without the potential confounds associated with task-related performances. More specifically, rs-fMRI is particularly suited to study the interaction between emotional and sensory/motor brain systems in clinical conditions in which it is challenging to collect task-based measures (e.g. dementia, severe motor deficits in patients with stroke, multiple sclerosis, or amyotrophic lateral sclerosis).

The present findings also provide support to the hypothesis that the amygdala may 'work in tandem with cortical sensory/motor areas to facilitate the preparation of adaptive responses to social and affective signals' (Grezes *et al.*, 2014). This is also consistent with previous task-based fMRI findings which found co-activation of the amygdala and sensory/motor cortices during emotional processing (de Gelder *et al.*, 2004; Ahs *et al.*, 2009; Pichon *et al.*, 2009; Schurmann *et al.*, 2011; Van den Stock *et al.*, 2011; Conty *et al.*, 2012; Grezes *et al.*, 2013; Kragel & LaBar, 2016), and with evidence from transcranial magnetic stimulation studies showing that emotional stimuli may facilitate action readiness (Oliveri *et al.*, 2003; Baumgartner *et al.*, 2007; Hajcak *et al.*, 2007; Toschi *et al.*, 2008, 2009; Coombes *et al.*, 2009; Coelho *et al.*, 2010).

In keeping with a recent DTI study (Grezes *et al.*, 2014), we found that the spontaneous activity in the dorsal amygdala, rather than in other amygdala nuclei, was functionally coupled with activity in the sensory and (pre)motor cortices at rest. This suggests that

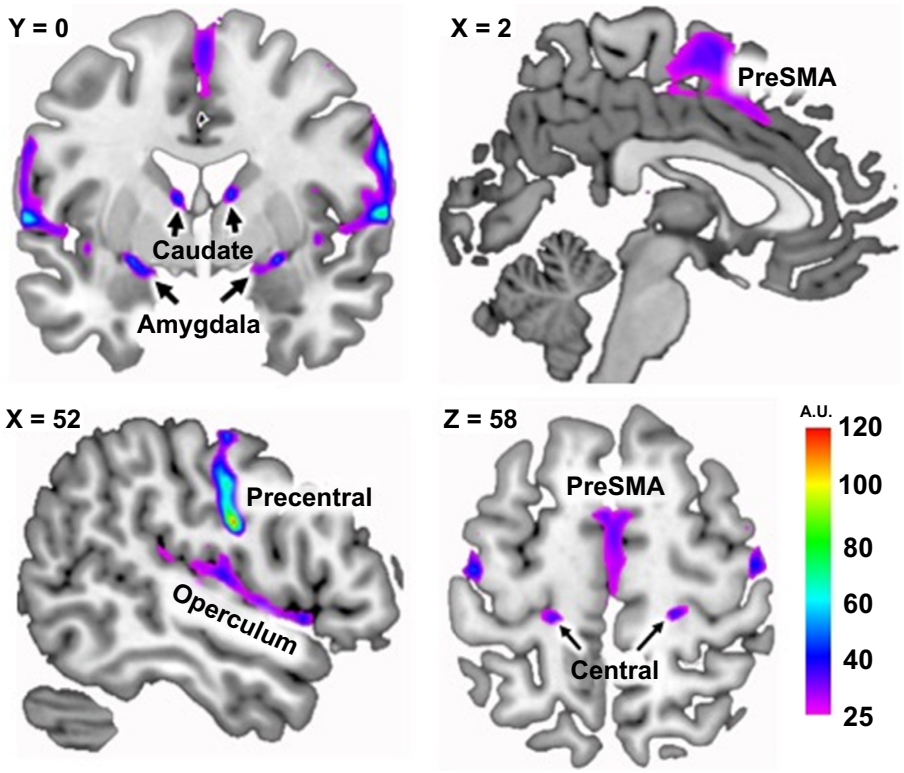

FIG. 1. Clusters remaining the 13th ICA component after thresholding at the 99th percentile. The colorbar shows the dual regression coefficient. Pre-SMA, pre-supplementary motor area; A.U., arbitrary units. [Colour figure can be viewed at wileyonlinelibrary.com].

TABLE 2. Anatomical Localization of topologically connected clusters after thresholding the 13th Independent Component Analysis (ICA) component within the 15 ICA set at the 99th percentile. Clusters sized 10 or less voxels were omitted

	Number of voxels	MAX	Hemisphere	MNI X	MNI Y	MNI Z
Primary Somatosensory Cortex (BA3)	1232	125	L	−54	−8	24
Primary Somatosensory Cortex (BA3)	1220	119	R	52	−6	26
Supplementary Motor Area (SMA)	138	39.1	R	2	2	64
Dorsal Amygdala	31	55.6	R	26	0	−10
Dorsal Amygdala	27	57.9	L	−26	−2	−10
Caudate Nucleus	27	50.7	R	10	0	12
Caudate Nucleus	27	51.5	L	−8	2	8
Primary Motor Cortex (BA4)	20	41.7	R	20	−28	58
Pre-SMA (BA6)	17	32.5	R	2	14	42
Primary Motor Cortex (BA4)	17	41	L	−18	−30	60

MAX, maximum value of dual regression coefficient within specific cluster. MNI, Montreal Neurological Institute. All coordinates are in mm. L, left hemisphere, R, right hemisphere.

the cortical sensory/motor system may be directly modulated by specific amygdalar output nuclei, which in turn receive highly processed inputs from other amygdalar circuits involved in emotional processing (e.g. the baso-lateral complex). However, just like the DTI results presented by Grezes *et al.* (Grezes *et al.*, 2014), our study does not enable to infer any directionality of the effects, which can only be examined using causal techniques for whole-brain rs-fMRI analysis (Duggento *et al.*, 2016). Nevertheless, given the prevalent presence of anatomical connections from the amygdala to pre-motor cortices rather than vice versa, it may be that the amygdala's influence over the sensory/motor cortical system is stronger than the opposite, although the motor areas are still in a position to significantly affect the amygdala function via other indirect and perhaps multi-synaptic pathways.

Assessing the amygdala/sensory-(pre)motor networks with rs-fMRI may also shed new light on to the pathophysiological mechanisms underlying a group of psychiatric, psychological, and neurological disorders in which movement control and action planning can be compromised by the presence of emotional dysfunction. Several studies have indeed found evidence that abnormal interactions between the amygdala and (pre)motor cortices may be at the basis of such disorders.

First, Voon *et al.* found increased functional connectivity between the amygdala and pre-motor regions (including SMA) in patients with conversion disorder (CD), relative to controls, while performing an emotional faces task (Voon *et al.*, 2010). Second, during both internally and externally generated movement, CD patients, relative to controls, have been reported to have lower SMA activity, which was associated with higher amygdala response (Voon *et al.*, 2011). Third, a recent meta-analysis of fMRI studies on motor conversion disorders (MCDs) found that MCDs patients differed from controls in a series of regions including the amygdala and primary motor cortex (Boeckle *et al.*, 2016). Fourth, convergent neuroimaging findings have suggested alterations in brain circuits mediating emotional processing (e.g. the amygdala) as well as motor control,

planning and coordination (e.g. SMA and cerebellum) in patients with psychogenic non-epileptic seizure, a MCD characterized by paroxysmal behaviors resembling epileptic seizures (Labate *et al.*, 2012; Perez *et al.*, 2015). Finally, a study in incarcerated young offenders found that the pre-motor cortex functional connectivity was correlated with activity in the default-mode network, a set of brain regions which includes medial temporal lobe areas like the hippocampus and amygdala (Shannon *et al.*, 2011).

At the same time, we have demonstrated that disease severity and duration in amyotrophic lateral sclerosis (ALS), a devastating motor neuron disease affecting motor and non-motor brain areas, was associated with progressively more abnormal functional connectivity between the amygdala and (pre)motor regions while processing emotional faces (Passamonti *et al.*, 2013). This is in keeping with previous neuropathological data showing that the amygdala, alongside the motor cortices, can be affected by neurodegeneration in ALS and may be critical in mediating some of the non-motor symptoms that characterize ALS (Takahashi *et al.*, 1997; Tsuchiya *et al.*, 2001, 2002). Furthermore, altered structural 'connectomic' measures including shortest path length between the amygdala and (pre)motor cortices were found in depressed patients with multiple sclerosis (MS), relative to non-depressed MS patients and controls (Nigro *et al.*, 2015). The existence of direct anatomical connections between the amygdala and sensory/(pre)motor cortices and the fact that these may have a functional relevance can thus provide a novel mechanistic explanation for the abnormal interactions between emotional and sensory/motor systems that can be detected in patients with ALS and MS.

In conclusion, although our study was performed in a high number of participants, whose data have been previously used to successfully delineate the main amygdalar output nuclei (Tyszka & Pauli, 2016), we cannot exclude a possible loss of spatial specificity due to partial volume effects. In addition, it should be noted that volumetric versions of subject-wise or group-wise Z or t maps from dual regression are not publicly available for analysis and, while single-subject Z-maps are available in gray-ordinate space, this space is not fully dense in subcortical regions, particularly around the amygdala. Therefore, in order not to omit the regions which are part of the key findings of this paper, we chose to work with the single volumetric, whole-brain average (across all subjects) maps. This motivated our choice of adopting a stringent 1% thresholding procedure of the group-wise map in lieu of group-wise statistical inference. Additional rs-fMRI studies in a broad spectrum of neuropsychiatric conditions as well as at ultra-high fields (7T) are now warranted to examine, with superior spatial resolution, how the disruption of the normal interactions between brain areas at the interface between the limbic and sensory-motor systems is associated with abnormal emotional behavior in different psychiatric and neurological diseases.

Supporting Information

Additional supporting information can be found in the online version of this article:

Fig. S1. This supplementary figure displays the entire extension of the activation clusters reported in Fig. 1.

Table S1. Anatomical Localization of topologically connected clusters after thresholding the 7th Independent Component Analysis (ICA) component with the 25 ICA set at the 99th percentile.

Table S2. Anatomical Localization of topologically connected clusters in each of the 15 Independent Component Analysis (ICA) components (from 1st to 15th excluding the 13th) after thresholding at the 99th percentile.

Conflict of interests

All of the authors have no conflicts of interest to declare.

Acknowledgements

Data were provided by the Human Connectome Project, WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University.

Data accessibility

The article supporting data and materials can be accessed at the following link: https://www.researchgate.net/profile/Luca_Passamonti.

Author contributions

Nicola Toschi: designed the study, analyzed data, and drafted the paper. Andrea Duggento: analyzed data. Luca Passamonti: designed the study, drafted the paper.

Abbreviations

ALS, amyotrophic lateral sclerosis; BA, Brodmann's area; BBR, boundary-based-registration; BOLD, blood–oxygenation–level–dependent; BW, band width; DTI, diffusion tensor imaging; FG, fusiform gyrus; HCP, Human Connectome Project; ICA, independent component analysis; MNI, Montreal Neurological Institute; MS, multiple sclerosis; OFC, orbitofrontal cortex; PCA, principal component analysis; rs-fMRI, resting-state, functional magnetic resonance imaging; SMA, supplementary motor area; STG, superior temporal gyrus; TE, echo-time; TR, repetition time.

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