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Consciousness in a multilevel architecture: Evidence from the right side of the brain

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ABSTRACT

By taking into account Bruce Bridgeman's interest in an evolutionary framing of human cognition, we examine effective (cause-and-effect) connectivity among cortical structures related to different parts of the triune phylogenetic stratification: archicortex, paleocortex and neocortex. Using resting-state functional magnetic resonance imaging data from 25 healthy subjects and spectral Dynamic Causal Modeling, we report interactions among 10 symmetrical left and right brain areas. Our results testify to general rightward and top-down biases in excitatory interactions of these structures during resting state, when self-related contemplation prevails over more objectified conceptual thinking. The right hippocampus is the only structure that shows bottom-up excitatory influences extending to the frontopolar cortex. The right ventrolateral cortex also plays a prominent role as it interacts with the majority of nodes within and between evolutionary distinct brain subdivisions. These results suggest the existence of several levels of cognitive-affective organization in the human brain and their profound lateralization.

1. Introduction

Two dominant vectors in the lifework of Bruce Bridgeman were studies of visual perception and the search for an evolutionary explanation of language, consciousness and cognition. BMV has benefited personally and scientifically from a long collaboration with Bruce Bridgeman. This collaboration was focused on the problems of visual psychophysics (e.g. Bridgeman, Van der Heijden, & Velichkovsky, 1994; Pannasch, Selden, Velichkovsky, & Bridgeman, 2011) but there was always our common interest in the evolution of consciousness and cognition in the background. When working on research papers, Bruce advocated for replacing undefined “it may be” by more the assertive “it can be” or even “it is”. We followed this recommendation in the present article, though it is devoted to still unresolved and highly speculative matters. From the early days of psychology and neurology, one particular approach to

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conceptualize mind evolution in terms of several evolutionary steps, or levels continuing to shape brain connectivity and cognitive-affective organization in the modern humans (Bridgeman, Cellier, Paillard, & Velichkovsky, 2000).

Presuming that there is such a “vertical dimension” of brain-and-mind functioning, what could the granularity and distinct characteristics of levels be? Over four decades ago, Gregory Razran (1971) reviewed more than 1500 studies on learning and memory, concluding that there must be a hierarchy of learning processes with several levels, which can be related to the evolutionary stage when they first appear. In another attempt to understand multiple stages of brain evolution, one of the founders of biomechanics, Nikolai Bernstein (1947), described four levels involved in construction of human movements: A. Paleokinetic regulation, B. Synergies, C. Spatial field, and D. Object actions. He linked the levels C and D to functions of parietal and temporal cortices. Bernstein also supposed that “one or two” levels of “higher symbolic coordinations” might be localized “above” level D, the Object actions. In their here-and-now functioning, levels are functionally organized in a temporary figure-ground structure. Depending on the task at hand, one of the levels, possessing operational resources with the best fit to ones demanded by the task solution, takes over the lead. This means that we are aware of the meaningful content of goals (the goals’ “what” but not “how”) that the currently leading level is pursuing. Other levels work in background mode whereby their operations remain unconscious. When the situation changes, any level may receive the leading status and therefore its goals become conscious. Considering this feature, Bernstein’s hierarchy is a heterarchy from the system theoretical point of view (Velichkovsky, 2002).

These early intuitions stemmed from biomechanical research and neuropsychological observations. Some of them have subsequently gained experimental support. For example, grasping movements show a dependence of finer object-adjusted hand movements (Bernstein’s level of objects action D) on the global translatory motion of the arm to a location in space (level of spatial field, or level C) (Jeannerod, 1997). As a whole, both of these hypothetical mechanisms in Bernstein’s theory strikingly resemble the dorsal and ventral pathways discussed in contemporary neuroscience (Parr & Friston, 2017; Ungerleider, & Haxby, 1994) and their respective ambient and focal modes of perceptual awareness (Velichkovsky, Joos, Helmert, & Pannasch, 2005). The functional imaging revolution in research methods has promoted the view of the brain as organized into a multilevel networks architecture, e.g. by description of two action counterparts to dorsal and ventral streams in perception (Fox, Corbetta, Snyder, Vincent, & Raichle, 2006). At the same time, the unified dorsal vs. ventral dichotomy is too narrow for a functional description of even the posterior parts of the human brain, especially with respect to functionality of the tertiary multimodal areas around the temporoparietal junction such as the right inferior parietal lobe (Singh-Curry, & Husain, 2009).

Of central relevance for our analysis is the discovery of a widely distributed network of brain structures, which is active during rest and inwardly-directed tasks such as contemplation, introspection and planning for the future (Gusnard, Akbudak, Shulman, & Raichle, 2001; Raichle, et al., 2001). This network is best known for its activation during conditions of relative rest and external inactivity and has thus been termed the Default Mode Network (DMN) (Raichle et al., 2001). The DMN comprises multiple interacting structures (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010). Most of them are located around the brain’s midline, like the medial prefrontal cortex, the posterior cingulate cortex, and the ventral precuneus, but the DMN also includes portions of the temporo-parietal junction, namely the left and right inferior parietal cortex (IPCl and IPCr, correspondingly). With respect to the hippocampal formation, rank correlations of activity have also revealed the basic pattern of activation/deactivation characteristic of the DMN (Greicius, Supekar, Menon, & Dougherty, 2009; Vincent, Bloomer, Hinson, & Bergmann, 2006). A number of hypotheses on the functionality of the DMN have been formulated mostly relating it to higher-order aspects of consciousness and self-related mental activities (Raichle, 2015; Schilbach, Eickhoff, Rotarska-Jagiela, Fink, & Vogeley, 2008).

Semiotic aspects of resting-state activity have not yet been studied systematically. In a pioneering brain mapping study of natural speech semantics, Alexander Huth and colleagues (Huth, de Heer, Griffiths, Theunissen, & Gallant, 2016) have recently demonstrated that the distribution of global semantic dimensions over the surface of the human cerebral cortex coincided with outlines of the DMN. Thus, the DMN could well suit the role of the upper-level mechanisms of “symbolic coordinations” anticipated by Bernstein (1947). Surprisingly, no leftward bias for natural speech categories was observed by Huth et al. (2016) but instead a broad distribution of semantic representations was found across both hemispheres. Moreover, an asymmetry for categories with attributes ‘mental’, ‘emotional’, and ‘social’ seemed to be present in the data with a focus around the right temporoparietal junction. The study used a flat projection of categories on the cortex and it is therefore impossible to determine whether underlying limbic structures such as hippocampus were involved.

The role of these structures can, however, be substantial as it has been shown in our study of effective (cause-and-effect) connectivity of the left and right hippocampal formation (HIPl and HIPr, respectively) within the DMN (Ushakov et al., 2016). In that study, we applied spectral Dynamic Causal Modeling (DCM) to resting-state functional magnetic resonance imaging (fMRI) data. The main idea of DCM is to evaluate parameters of a biologically validated model of the neuronal system so that it can predict the observed fMRI data in the best way (Friston, Kahan, Biswal, & Razi, 2014; Sharaev, Zavyalova, Ushakov, Kartashov, & Velichkovsky, 2016). Our study was conducted in a group of 30 healthy right-handed subjects and comprised the DCM analysis of two 5-nodes and one 6-nodes interactions. The winning models demonstrated a significant asymmetry in the effective connectivity between hippocampi and the main multimodal regions of the posterior neocortex, IPCl and IPCr. While HIPl demonstrated bidirectional interaction with IPCl, there was no inflow to HIPl from IPCr. This means that in terms of spatial representation HIPl has access to information only from the right hemisphere of the surrounding. On the contrary, HIPr was affected by inputs from both IPCl and IPCr that could lead to a holistic multimodal representation including both hemispheres (for a detailed analysis, see Ushakov et al., 2016).

The pattern of causal relationships characteristic of the hippocampal formation can be important for a causal explanation of various neglect phenomena and for a possible division of the brain mechanisms depending on their evolutionary origin in two or more large-scale functional groups, *aka* levels. In the present study, we extended our analysis of lateralization in effective connectivity under resting state beyond the borders of the core DMN, by including in a series of spectral DCM analyses interactions

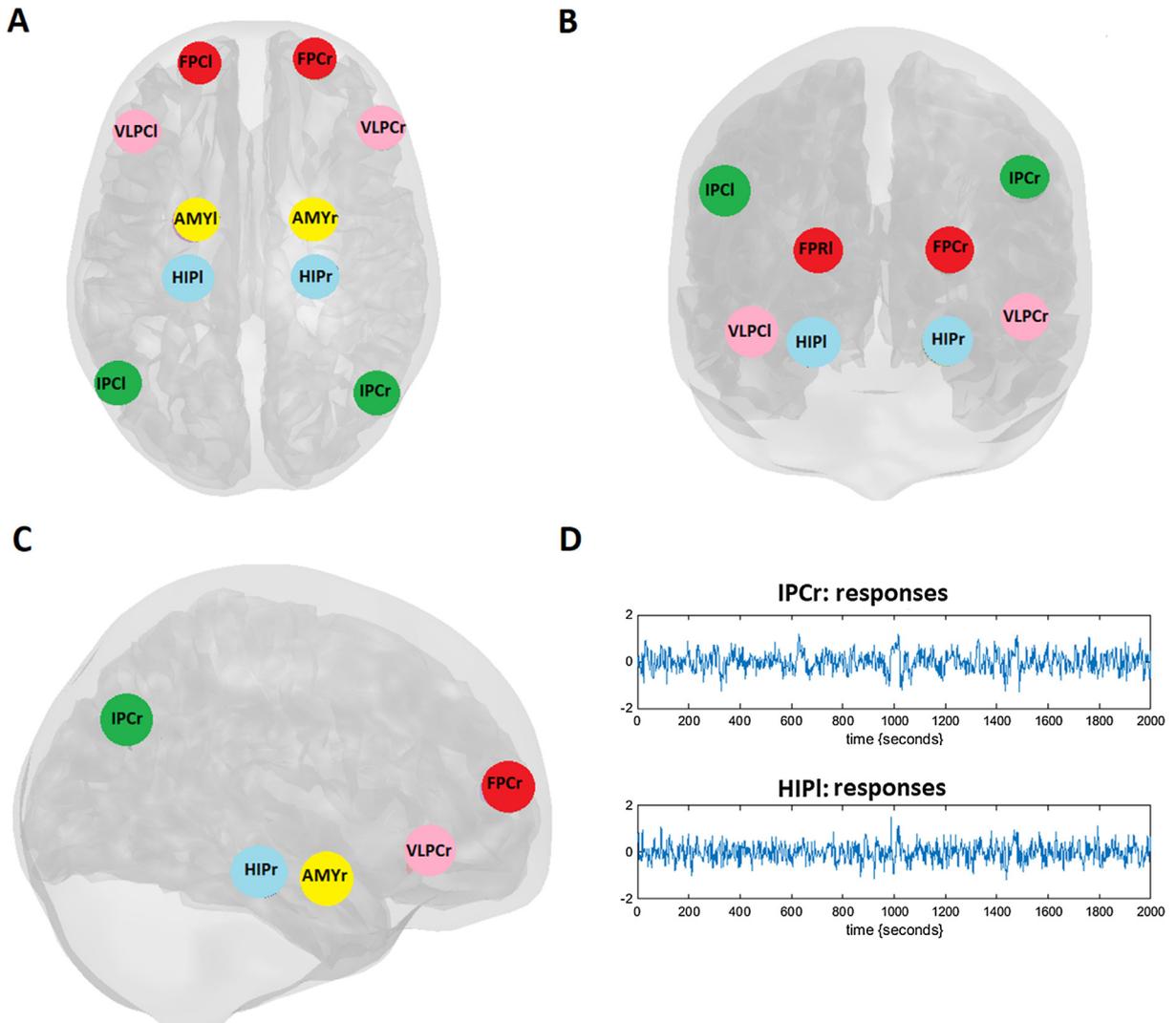


Fig. 1. Locations of the 10 investigated source ROIs in axial (A), coronal (B), and right-sided sagittal (C) projections of the brain. The regions are identified using a conventional SPM analysis. Corresponding time-series for two exemplary ROIs are principal eigenvariables of regions (D).

between left and right parts of several regions symmetrical across the brain's midline. We selected regions of interest (ROIs) according to their ascription to evolutionarily different subdivisions of the human cortex (Luria, 1966; Mega, Cummings, Salloway, & Malloy, 1997). The neocortex was represented by frontopolar cortices (FPCl and FPCr, also known as rostral prefrontal cortex or zone BA10, in Brodmann classification), ventrolateral prefrontal cortices (VLPCl and VLPCr), and, in the posterior part, by IPCl and IPCr. The paleocortex was represented by both amygdalae (AMYl and AMYr). Finally, the archicortex was represented by the hippocampal formation, i.e. HIPl and HIPr. The exact localization of these ROIs in MNI coordinates is provided in the next section and shown approximately in Fig. 1A–C.

Our *a priori* expectation was to find several interaction trends among structures as revealed by causal modeling. Specifically, a first possible trend is a dominance of leftward causation, from the verbal and dominant left hemisphere to the spatial subdominant right hemisphere (Kolb, & Whishaw, 2015). Secondly, we expected a generally top-down direction of influence in hierarchical architectures, i.e., from neocortex, to paleocortex and to archicortex. Earlier data, on functional interaction between prefrontal areas and limbic brain structures, e.g. the ventrolateral prefrontal-amygdala emotional pathway, demonstrated the existence and asymmetry of such connections (Kerestes, Chase, Phillips, Ladouceur, & Eickhoff, 2017) but not in terms of direction and intensity of causation as the latter information could be elucidated only by instruments for analysis of effective connectivity, such as spectral DCM. Despite a growing interest in this and other neural circuits along the vertical dimension of brain organization, recent meta-analytic studies do not provide data on causal interactions (Di, Huang, & Biswal, 2017; Marusak et al., 2016). This lack of knowledge about effective connectivity of prefrontal and limbic structures during resting state was a primary motivation for the present study.

2. Materials and methods

2.1. Subjects

MRI data was obtained from 25 healthy subjects (11 males and 14 females, all right-handed without neurological symptoms), mean age 24 years (20–35 years). Informed consent was obtained from each participant. All participants were asked to maintain wakefulness during the study, as those who fell asleep in scanner would be excluded from the study. Permission to undertake this experiment was granted by the Ethics Committee of the Institute of Higher Nervous Activity and Neurophysiology of the Russian Academy of Sciences.

2.2. Scanning parameters

Since spectral DCM (root) mean square error decreases as the number of time points increases, based on results from (Razi, Kahan, Rees, & Friston, 2015) we decided to acquire 1000 time points (with a repetition time of 2 s) resulting in approximately 35 min of scanning. The MRI data was acquired using a 3 Tesla SIEMENS Magnetom Verio MR tomograph. The T1-weighted sagittal 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence was acquired with the following imaging parameters: 176 slices, TR = 1900 ms, TE = 2.19 ms, slice thickness = 1 mm, flip angle = 9°, inversion time = 900 ms, and FOV = 250 × 218 mm². fMRI data was acquired as T2*-weighted echo-planar images (EPIs) with the following parameters: 30 slices, TR = 2000 ms, TE = 25 ms, slice thickness = 3 mm, flip angle = 90°, and FOV = 192 × 192 mm². A map of magnetic field inhomogeneities was acquired for each subject to optimize correction for spatial distortions of EPIs (see below).

2.3. Imaging data analysis

The fMRI and anatomical MR data were pre-processed using Statistical Parametric Mapping (SPM12; Wellcome Trust Centre for Neuroimaging, London, UK; available free at <http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>) based on Matlab 2016a. After importing the Siemens DICOM files into the SPM NIFTI format, the center of anatomical and functional data was manually set to the anterior commissure for each subject. Spatial distortions of the EPIs resulting from motion-by-field inhomogeneity interactions were reduced using the FieldMap toolbox implemented in SPM12 (Friston, Ashburner, Kiebel, Nichols, & Penny, 2007). Next, slice-timing correction for fMRI data was performed (the correction of the hemodynamical response in space and then in time to avoid pronounced motion artifacts; Sladky et al., 2011). Anatomical MPRAGE images were segmented using the segmentation algorithm implemented in SPM, and both anatomical and functional images were normalized into the ICBM stereotactic reference frame using the warping parameters obtained from segmentation. Functional data was smoothed using a Gauss function with an isotropic kernel of 6 mm FWHM.

The amygdala mask was created in WFU pickatlas (Wake Forest University; freely available at <http://fmri.wfubmc.edu/software/pickatlas>). The masks based on this atlas also contained other regions in the right and left hemisphere: Brodmann areas 19 and 39, as well as parahippocampal gyrus (Di & Biswal, 2014; Jann, Kottlow, Dierks, Boesch, & Koenig, 2010). Separate masks for the frontopolar prefrontal cortex (FPC, BA10 in Brodmann classification) and ventrolateral prefrontal cortex (VLPC, Brodmann areas 44, 45, 47) in both hemispheres were created using the MARSBAR toolbox (Brett et al., 2002) in the SPM8 version (freely available at <http://marsbar.sourceforge.net/>).

The resting state was modeled using a General Linear Model with a discrete cosine basis set (GLM-DCT) consisting of 400 functions with frequencies characteristic of resting state dynamics of 0.0078–0.1 Hz (Biswal, Yetkin, Haughton, & Hyde, 1995; Deco, Jirsa, & McIntosh, 2011), as well as six nuisance regressors from each session capturing head motion, and the confound time-series from the extra-cerebral compartments. An F-contrast was specified across all frequencies of DCT, producing a statistical parametric map (SPM) that identified regions exhibiting BOLD fluctuations within the frequency band. The preprocessing and conventional SPM analyses are the same as in our previous work assessing the effective connectivity between four key DMN regions (Sharaev, et al., 2016).

The obtained statistical parametric maps were then masked with previously created masks for FPC, VLPC amygdalae and DMN. Next, the intersection of mask and statistical map was used for time-series extraction, using an additional grey matter mask in the case of deep brain structures. In the current work, we used the DMN mask only to extract time-series from inferior parietal cortex and parahippocampal gyrus separately for the left and right hemispheres. As described previously (Ushakov et al., 2016), the principal eigenvariates of the time-series were extracted from spheres (8 mm radius) centered at the appropriate MNI coordinates of the respective DMN subregions: IPCl [−50, −63, 32], IPCr [48, −69, 35], HIPl [−22−23 −14] and HIPr [19−20 −10] (see also functional DMN data in Jann et al., 2010). Because the hippocampus is an extended and heterogeneous structure, we aimed to assess whether connectivity patterns change when selecting another portion of the hippocampus for analysis. To this end, we extracted time-series from symmetrical parts of both hippocampi: HIPl [−22−23 −14] and HIPr [22−23 −14] in the same manner as earlier, by using principal eigenvariates of 8 mm spheres. Amygdalae in left and right hemispheres were considered with center coordinates AMYl [−22−4 −18], AMYr [22−4 −18]. Time-series from both FPC and VLPC were extracted from appropriately masked SPMs (without additional sphere assignment), i.e. we extracted the principal eigenvariates from entire Brodmann areas. The number of activated voxels in the ROIs across all subjects ranged from 20 in small areas like amygdala to more than 1500 in large areas like the FPC. Fig. 1(A–C) shows the locations of all ROIs of the present study. Examples of time series (from two of the 10 ROIs – IPCr and HIPl) are shown in Fig. 1D.

Table 1

Mean connection strengths (in Hz) of the FPCl/FPCr-VLPCL/VLPcR interaction (one-sample *t*-test, 24 subjects). Source regions are displayed in the rows, target regions in columns. Non trivial significant ($p < 0.05$) connections are marked in bold, significant connections that survived Bonferroni correction are additionally marked with an asterisk (*).

<i>t</i> -test	From FPCl	From FPCr	From VLPCL	From VLPcR
to FPCl		0.28*	0.07	0.14
to FPCr	0.18		0.01	0.39*
to VLPCL	0.02	0.03		0.38*
to VLPcR	-0.05	0.16	0.01	

In order to explore the effective connectivity within the limbic system as well as between parts of the limbic system and neocortex, we decided to split the vast model space into groups of simpler models with only 4 nodes (Ushakov et al., 2016). This was done to minimize estimation and convergence problems due to high model complexity (number of free parameters). The first group of models was dedicated to interaction among 4 prefrontal nodes: left and right FPC (FPCl/FPCr) and VLPC (VLPCL/VLPcR). The second group was designed to study FPC-IPC interaction, the third group – to study VLPC-IPC interaction, the fourth group – to study FPC-amygdalae interaction, the fifth group – to study FPC-hippocampi interaction, the sixth group – to study VLPc-amygdalae interaction, the seventh group – to study VLPc-hippocampi interaction, the eighth group – to study IPC-amygdalae interaction, the ninth group – to study IPC-hippocampi interaction, and the tenth group – to study amygdalae-hippocampi interaction.

All models were inverted in SPM12 (v6906) with no external input in the spectral domain. Some subjects did not reveal significant activity in particular ROIs, therefore data of these subjects were removed from the group analysis for only those models that contained the respective ROIs as nodes. After full model inversion, post-hoc optimization was performed (function `spm_dcm_post_hoc.m`) and the reduced models which explained more than 80% of the variance (sanity check `spm_dcm_fmri_check.m`) were selected for group analysis: one sample *t*-tests were conducted to examine whether these parameters have significantly nonzero values (Friston, et al., 2014). For each significant group value, Bonferroni correction was performed to test it on survival.

3. Results

The results of statistical *t*-tests on optimized models are shown in Tables 1–10 below, separately for each group of models. To focus on non-trivial connections, we only report results on particular connections when their strengths exceed 0.1 Hz. For simplicity reasons, we also do not report self-connections in graphs. For each group result, the number of considered subjects is reported in the respective table caption. As stated above, only subjects who demonstrated activation in ROIs and whose models explained more than 80% of variance were considered for group analyses.

To achieve a more comprehensive picture of the results, we present them next in a graphical form whereby only non-trivial significant connections that survived Bonferroni correction are selected and the evolutionary framing reflected in the three subdivisions of the human cortex is introduced explicitly. In the latter case, we decided to additionally divide the neocortical ROIs into groups of nodes with anterior (FPCl/FPCr, VLPCL/VLPcR) and posterior (IPCL/IPCr) localization. Fig. 2 shows those effective connections of brain areas that served as ROIs located solely *within* the neocortex, the paleocortex, or the archicortex.

In contrast to the previous picture, Fig. 3 shows the discovered effective connections *between* these phylogenetically different subdivisions of the human cortex. As mentioned above, the interaction of the posterior neocortical structures IPCL and IPCr with both hippocampi has been extensively investigated previously under similar resting-state conditions in a larger group of healthy subjects of approximately the same age as in the present study (Ushakov et al., 2016). For the sake of comparison, these earlier results with a slightly different location of the referential HIPr node (the shift of about 6 mm in ventral direction) are also presented in Fig. 3.

The overall pattern of results is rather consistent. Firstly, all the revealed effective connections are excitatory. Secondly, they predominantly show a right-to-left direction of influence. With respect to interaction between the subdivisions of the human cortex, the majority of these connections are of the top-down kind, although there is one notable exception related to ascending influence of HIPr on a number of structures. As can be seen from Fig. 3, the exact location of selected ROIs within such extended brain structures as the hippocampal formation is of relevance. In the present study, ROI location changes the merely inflow pattern of interactions into an outflow one. We combine a more detailed description of the results with their interpretation in the next section.

Table 2

Mean connection strengths (in Hz) of the FPCl/FPCr-IPCL/IPCr interaction (one-sample *t*-test, 21 subjects). Source regions are displayed in the rows, target regions in the columns. Non-trivial significant ($p < 0.05$) connections are marked in bold, significant connections that survived Bonferroni correction are additionally marked with asterisk (*).

<i>t</i> -test	From FPCl	From FPCr	From IPCL	From IPCr
to FPCl		0.39*	0.22*	-0.01
to FPCr	0.12		0.04	0.14
to IPCL	-0.05	0.06		0.15
to IPCr	-0.08	0.14	0.15	

Table 3

Mean connection strengths (in Hz) of the FPCI/FPCr-IPCI/IPCr interaction (one-sample *t*-test, 21 subjects). Source regions are displayed in the rows, target regions in the columns. Non-trivial significant ($p < 0.05$) connections are marked in bold, significant connections that survived Bonferroni correction are additionally marked with asterisk (*).

<i>t</i> -test	From VLPCI	From VLPCr	From IPCI	From IPCr
to VLPCI		0.36*	0.10	-0.04
to VLPCr	-0.04		-0.15	0.05
to IPCI	0.06	0.18		0.16
to IPCr	-0.13	0.28*	0.16	

Table 4

Mean connection strengths (in Hz) of the FPC-amygdalae interaction (one-sample *t*-test, 19 subjects). Source regions are displayed in the rows, target regions in the columns. Non-trivial significant ($p < 0.05$) connections are marked in bold, significant connections that survived Bonferroni correction are additionally marked with asterisk (*). Group size is 19 subjects.

<i>t</i> -test	From FPCI	From FPCr	From AMYI	From AMYr
to FPCI		0.27*	0.02	0.02
to FPCr	0.03		0.06	0.02
to AMYI	-0.01	0.05		0.21
to AMYr	-0.01	0.11	0.11	

Table 5

Mean connection strengths (in Hz) of the FPC-HIP interaction (one-sample *t*-test, 19 subjects). Source regions are displayed in the rows, target regions in the columns. Non-trivial significant ($p < 0.05$) connections are marked in bold, significant connections that survived Bonferroni correction are additionally marked with asterisk (*).

<i>t</i> -test	From FPCI	From FPCr	From HIPI	From HIPr
to FPCI		0.19	0.02	0.03
to FPCr	0.03		-0.02	0.24*
to HIPI	-0.09	0.17		0.23
to HIPr	-0.09	0.11	-0.00	

Table 6

Mean connection strengths (in Hz) of the VLPC-amygdalae interaction (one-sample *t*-test, 20 subjects). Source regions are displayed in the rows, target regions in the columns. Non-trivial significant ($p < 0.05$) connections are marked in bold, significant connections that survived Bonferroni correction are additionally marked with asterisk (*).

<i>t</i> -test	From VLPCI	From VLPCr	From AMYI	From AMYr
to VLPCI		0.27*	0.11	0.04
to VLPCr	0.00		-0.07	0.04
to AMYI	-0.09	0.22		0.23*
to AMYr	-0.14	0.32*	0.17	

Table 7

Mean connection strengths (in Hz) of the VLPC-HIP interaction (one-sample *t*-test, 19 subjects). Source regions are displayed in the rows, target regions in the columns. Non-trivial significant ($p < 0.05$) connections are marked in bold, significant connections that survived Bonferroni correction are additionally marked with asterisk (*).

<i>t</i> -test	From VLPCI	From VLPCr	From HIPI	From HIPr
to VLPCI		0.34*	-0.02	0.00
to VLPCr	-0.02		-0.04	0.03
to HIPI	-0.07	0.23		0.22
to HIPr	0.02	0.21	0.03	

4. Discussion

The present study has revealed a number of asymmetries between the left and right hemispheres in the investigated parts of the neocortex and limbic system during resting-state conditions. The lateralization of the neocortex has been a well-established phenomenon since the seminal works of Paul Broca and other authors, who observed that the left hemisphere dominates in speech production and in the control of voluntary movements. Our finding is novel because it also refers to an asymmetry in the relation

Table 8

Mean connection strengths (in Hz) of the IPCI/IPCr-amygdalae interaction (one-sample *t*-test, 20 subjects). Source regions are displayed in the rows, target regions in the columns. Non-trivial significant ($p < 0.05$) connections are marked in bold, significant connections that survived Bonferroni correction are additionally marked with asterisk (*).

<i>t</i> -test	From IPCI	From IPCr	From AMYl	From AMYr
to IPCI		0.17*	-0.07	0.09
to IPCr	0.22*		-0.16	0.09
to AMYl	0.10	-0.07		0.23*
to AMYr	0.10	-0.03	0.01	

Table 9

Mean connection strengths (in Hz) of the IPCI/IPCr-hippocampi interaction (one-sample *t*-test, 20 subjects). Source regions are displayed in the rows, target regions in the columns. Non-trivial significant ($p < 0.05$) connections are marked in bold, significant connections that survived Bonferroni correction are additionally marked with asterisk (*).

<i>t</i> -test	From IPCI	From IPCr	From HIPl	From HIPr
to IPCI		0.13	-0.09	0.17
to IPCr	0.14		-0.14	0.10
to HIPl	0.12	-0.05		0.34*
to HIPr	0.13	0.00	0.01	

Table 10

Mean connection strengths (in Hz) of the amygdalae-HIPl/HIPr interaction (one-sample *t*-test, 18 subjects). Source regions are displayed in the rows, target regions in the columns. Non-trivial significant ($p < 0.05$) connections are marked in bold, significant connections that survived Bonferroni correction are additionally marked with asterisk (*).

<i>t</i> -test	From AMYl	From AMYr	From HIPl	From HIPr
to AMYl		0.22*	-0.04	0.08
to AMYr	0.10		-0.14	0.19*
to HIPl	-0.01	0.16		0.20*
to HIPr	-0.08	0.15	0.12	

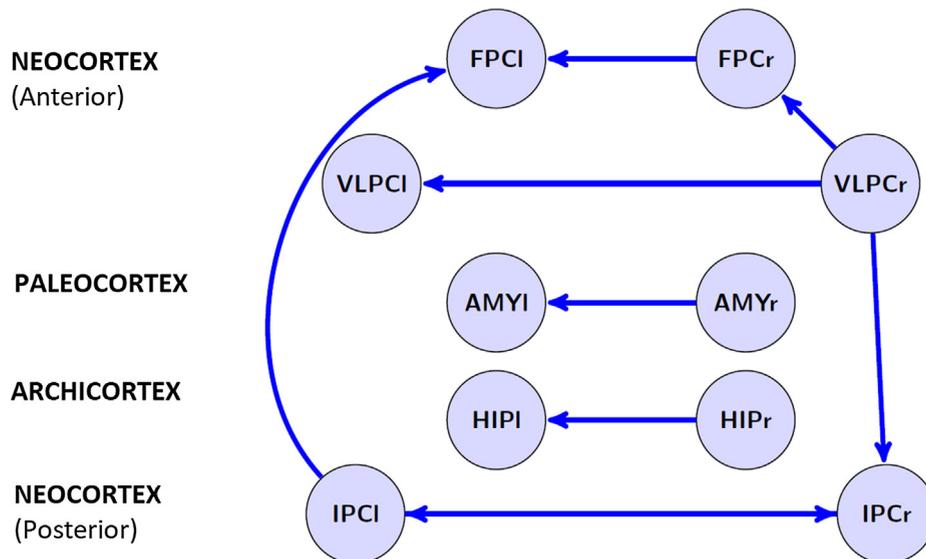


Fig. 2. Statistically significant effective connections of brain areas served as ROIs that are located solely *within* the neocortex, the paleocortex, or the archicortex all links are excitatory.

between subdivisions of the limbic system, or, more specifically, the phylogenetically deep structures of amygdala (paleocortex) and the hippocampus (archicortex). Moreover, with the overall rightward bias of the excitatory connections, the direction of influence is opposite to the one generally expected before, i.e. from the presumably 'dominant' left hemisphere to the 'subdominant' right hemisphere.

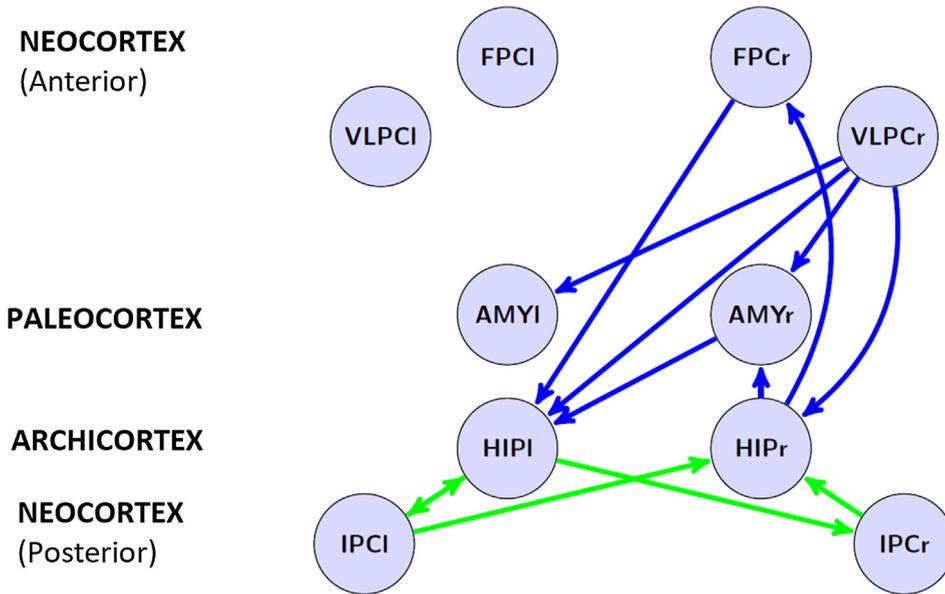


Fig. 3. Statistically significant effective connections of brain areas served as ROIs that are located *between* the neocortex, the paleocortex, and the archicortex. Green arrows in the lower part of the scheme show an interaction of hippocampi with IPC and a different ROI localization (after Ushakov et al., 2016). All links are excitatory. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

We consider at first interactions of limbic structures observed in our study. Taking into account our previous results, namely data of the 6-nodes interactions within the DMN (Ushakov et al., 2016), we tentatively conclude that left and right hippocampi are in mutual excitatory interaction. Differences in interaction patterns depending on mask choice for HIPr are not surprising with regard to the high heterogeneity of the hippocampal formation as a structure strongly involved in representation of surrounding space (Burgess, Jackson, Hartley, & O’Keefe, 2000; Moser, & Moser, 2008), in episodic memory processes (Dickerson, & Eichenbaum, 2010), and probably in self-related cognition (Velichkovsky, Krotkova, Sharaev, & Ushakov, 2017; Zhu et al., 2012). Neocortical input regarding the object identities (‘what’) converges in the perirhinal cortex and lateral entorhinal area, whereas details about the location (‘where’) of objects converge in the parahippocampal cortex and medial entorhinal area. These pathways come together in the hippocampus, which represents items in the context in which they were experienced (Eichenbaum, Yonelinas, & Ranganath, 2007). For the hippocampal masks used in this and previous studies an egocentric spatial representation typical for the ‘where’ system can be expected (Neggers, Van der Lubbe, Ramsey, & Postma, 2006).

The next limbic structure of this study is the amygdala. Both amygdalae exhibit an interaction pattern rather similar to that of hippocampi, with a stronger and more systematic influence of the right hemisphere structures on the left than vice versa. There is a strong top-down influence of AMYr on HIPl, and an ascending influence of HIPr on AMYr. Thus, amygdalae and hippocampi show a similar pattern of interactions at rest, even though they can be well dissociated in task situations, particularly under influence of negative emotions (Bisby, Horner, Hørlyck, & Burgess, 2016).

Data of our effective connectivity analysis extended beyond the borders of limbic system and the core DMN confirm the trend towards an overall rightward dominance of cause-and-effect influences during the resting state. The right VLPC has an excitatory influence on VLPCI and FPCr as well as on both amygdalae and hippocampi. It is a structure with the most of outflow causal links discovered in the present study. Within the anterior prefrontal cortex, we find a strong dominance of FPCr over its left counterpart. This lateralization in the functioning of the FPC is echoed in results of new transcriptomic studies (Dolina et al., 2017), where a right-sided predominance in the differential expression of protein-coding genes was established. There is also influence of FPCr on HIPl. On the other hand, no interaction of the FPC with the amygdalae has been found. As a whole, our data confirm the hypothesis about mostly top-down causal links in a hierarchical architecture as we were unable to find any effective connection directed from the limbic structures tested in this study to the prefrontal cortex. The only remarkable exception to this rule is an excitatory influence of HIPr on FPCr and AMYr. A pronounced pattern of asymmetry in functional connectivity of prefrontal cortex and amygdalae was recently reported by Kerestes, et al. (2017) who found all correlative links in their study concentrated on AMYr independently on its specific parts.

Of importance for our discussion is the observed connectivity of the FPC. From a phylogenetic point of view, the FPC is the most rapidly growing brain area, increasing its relative size by factor 10 during the hominid evolution (Semendeferi, Armstrong, Schleicher, Zilles, & Van Hoesen, 2001). Histological analysis testifies to a special status of the FPC, which possesses a low neuronal density but an unusually high density of dendritic spines (Jacobs et al., 2001; Semendeferi et al., 2011). Such an organization has been suggested to be particularly suitable for its role as a higher-order integrator of information (Burgess & Wu, 2013). According to the present results, the FPC not only exerts a strong outflow influence on number structures but also is under influence of VLPCr, IPl, and IPCr.

and HIPr. Studies of large-scale networks of the human brain show that the FPC does not belong to either the DMN or its anticorrelated counterpart, the antiDMN (Di Perri et al., 2016), which is a pool of structures inhibited at rest and activated by outwardly directed tasks. The antiDMN borders the FPC, the DMN, and primary sensory-motor zones (Verkhlyutov, Sokolov, Ushakov, & Velichkovsky, 2017) and seems to play a major integrative role similar to that of DMN, but in relation to perception of the external world and behavioral reactions to it involving, for instance dorsal and ventral attention systems (similar to Bernstein's levels C and D). In such a gross multilevel picture the FPC can coordinate external and inner forms of activity. Burgess and Wu (2013) proposed that its core function can be best described as "metacognition". One of us has used a similar expression "metacognitive coordination" to describe the function of the upper level in the brain cognitive organization attributed to right prefrontal structures (Velichkovsky, 2002). In the view of our current knowledge, this attribution is only partially correct. It is correct in emphasizing the role of rightward bias, for which we find strong evidence under resting state. However, the attribution is insufficient because it does not take into account the diversity of lateralization phenomena and an involvement of structures localized "behind and below" of anterior prefrontal cortex.

Suggestions for right hemisphere dominance can be found in a variety of domains. For example, studies of active vision have shown that the exploration of complex scenes begins with an ambient mode of processing (short visual fixations and long-range saccades), which within a few seconds proceed to a more attentive, or focal mode of processing (Ito et al., 2017; Unema, Pannasch, Joos, & Velichkovsky, 2005; Velichkovsky, Rothert, Kopf, Dornhoefer, & Joos, 2002). Follow-up studies have demonstrated that this ambient-to-focal shift temporally overlaps with a shift of activity from the right to the left hemisphere suggesting a rightward dominance in the early phase of spatial orientation (Mills et al., 2017). Similar rightward lateralization has been found with respect to the human mirror neuron system (Aziz-Zadeh, Koski, Zaidel, Mazziotta, & Iacoboni, 2006). Brain activation during limb movements is typically lateralized to the contralateral hemisphere. However, this is not the case during *illusory* limb movements, as in the tendon vibration illusion: stronger activation have been observed here in the right hemisphere independent on whether the left or right hand was involved (Naito et al., 2005). In clinical context, disorders of spatial, corporeal, emotional and self-related consciousness primarily results from lesions of the right hemisphere (Harrison, 2015; Howard, & Templeton, 1966; Luria, 1966). A neurolinguistic pendant to these data is the well-established knowledge that, while the left hemisphere supports basic linguistic functions in the vast majority of humans, the right prefrontal cortex is important for understanding of communication pragmatics, metaphorical language, humor, irony and sarcasm (Kaplan, Brownell, Jacobs, & Gardner, 1990; Shammi, & Stuss, 1999). Moreover, the right prefrontal areas are preferentially involved in retrieval of autobiographical memories, personally-related encoding of information, and planning for the future (Craik et al., 1999; Dickerson, & Eichenbaum, 2010; Habib, Nyberg, & Tulving, 2003; Velichkovsky, Klemm, Dettmar, & Volke, 1996). These processes are directly related to our subjectively colored experience, i.e., to our conscious «self».

The picture of prefrontal involvement in the higher-order cognitive processing is appealing but it is incomplete. Posterior brain regions nearby the temporoparietal junction, first of all IPCr, seem to realize similar functions with respect to self-related cognition. Basically, these are structures of higher-order multimodal sensory integration. Such multimodal nature is demonstrated by spatial neglect phenomena (Vallar, Bottini, & Sterzi, 2003) that cannot be reduced to only visual modality (Parr, & Friston, 2017). Distortions of corporeal awareness such as out-of-body experience (Blanke, & Mohr, 2005), asomatognosia (Baier, & Karnath, 2008) and anosognosia (Heilman, 2014) have also been described in patients with the same loci of lesions in both anterior and posterior parts of the right hemisphere. We recently described two qualitatively different patterns in everyday behavior and test performance in patients with damage in either left or right tertiary areas in the posterior cortex: 45 persons with lesions localized in IPCr and 58 persons with lesions in IPCr (Velichkovsky et al., 2017). Despite interindividual variability and interference from other deficits, the two patterns were very distinct. IPCr patients tended to overestimate the actual complexity of their surrounding world of things and standard social situations, whereas IPCr patients were prone to simplifying social interactions by failing to experience mental states and to attribute these states to other people. In clinical context, a tendency to simplify the social world may, in extreme cases, manifest at psychotic delusions. Dysfunction of the interactions between HIPr and orbitofrontal cortex during novelty processing have been implicated in the pathogenesis of delusions in schizophrenia (Schott, et al., 2015), and right hemispheric lesions prevail among patients with psychotic symptoms related to structural brain damage (Gurin & Blum, 2017).

Our present results provide evidence for a right-to-left bias of effective connections during resting state, when self-related contemplation prevails over more objectified conceptual thinking (Gusnard, et al., 2001; Raichle, 2015; Schilbach et al., 2008). This suggests that there may actually be two distinct levels of organization with lateralized brain mechanisms behind them, or "two levels of higher symbolic coordination". Correspondingly and in tune with Bernstein's tradition, they can be named, *Level of Conceptual Structures* (Level E) and *Level of Personal Sense* (Level F). In this configuration, the FPC seems to be a relatively higher-order structure. In agreement with Burgess and Wu (2013), its core function within the Grand Design of brain cognitive-affective organization can be described as *Level of Metacognition*. Whether it might also be "Level G" or perhaps "Level H" is an open question at the moment, the answer to which will depend on future connectivity studies of prefrontal structures at rest and during task performance. In our set of data, one sees in particular an outstanding role of VLPCr as the major intersection of causal links. Apparently, this part of the ventrolateral prefrontal-amygdala emotional pathway ties the whole multilevel resting-state network together.

Where does the bias towards the right hemisphere causation of self-related processing come from? We incline to explain this by the asymmetry in the effective connectivity of the hippocampal formation (Ushakov et al., 2016). The person's relative spatial location might be represented in the hippocampal formation, more on the right than on the left side, serving as the basis for further accumulation of self-related information well beyond the metrics of egocentric space. Broad integration from distributed parts of cortex and multimodality of clinical effects show that HIPr can have the function of a "sensus communis", i.e. the major gateway for processes of self-referential cognition, emotional and corporeal awareness (Velichkovsky et al., 2017). Structural data also demonstrate that, in average, HIPr has a larger volume in comparison to HIPl (Shi, Liu, Zhou, Yu, & Jiang, 2009). As to behavioral measures,

the IPCr and HIPr resting-state fMRI data are the best predictors of working memory performance traditionally associated with the field of consciousness, the scope of the content which we are aware of at the present moment and in the absence of physical stimulation (Doucet et al., 2015; Markett et al., 2017). Finally, there are new studies demonstrating how spatial cognitive maps within the hippocampal formation can be transformed into conceptual representations (Kaplan, Schuck, & Doeller, 2017).

With respect to the left hemisphere's functions, it has to be noted that task instructions – even if they leave unchanged the overall inward orientation of processing – are realized via left-sided inhibitory connections (Soch et al., 2017; Ushakov et al., 2016). A weak trend towards leftward lateralization of inhibitory connections under resting state can become stronger in explicit task situations. During memory encoding, for example, the task-related functional connectivity between the HIPr and the IPCr has previously been shown to correlate with the level-of-processing effect, i.e. the mnemonic advantage for semantically compared to non-semantically processed verbal information (Schott et al., 2013). This picture resembles the division of labor postulated in the neuropsychological ROBBIA model based on a test battery of prefrontal cortex dysfunction (Ambrosini, & Vallesi, 2016; Stuss, Rosenbaum, Malcom, Christiana, & Keenan, 2005). Specifically, Stuss and Alexander (2007) have distinguished a “left-lateralized” task-setting function, defined as transient cognitive control, from a “right-lateralized” monitoring function, which is needed to actively maintain abstract representations. Thereafter, one can expect that the task-setting function can be primarily realized through inhibitory causal connections. The follow-up research is needed to test this prediction and additionally integrate emerging views of hierarchical organization with a variety of hemispheric specializations (Margulies, & Smallwood, 2017; Zhou, Friston, Zeidman, Chen, Li, & Razi, 2017).

Resting-state mentalizing, which seems to be dominated by the right hemisphere of the brain in terms of effective connectivity, is overtly self-related. According to Huth et al. (2016) study, the natural speech semantic representations are broadly distributed across both hemispheres. Why then is the left-sided contribution so weak in our results? An answer is that these representations remain largely unconscious during the resting state or, in other terms, they are hidden in the background of the leading level (Level F, in the case) activity. When the situation changes, for example, when we have to write an article and start to search for an appropriate title in the mental lexicon, some of the hidden relationships of natural language semantics and grammar (they are belonging to the domain of expertise of Level E) came to the focus of consciousness, while countless connections, such as related to personal worries, memories and intentions, disappear in the background.

Such rather trivial first-person observations can be of scientific relevance. Different forms of consciousness are nowadays considered results of computation (Dehaene, Lau, & Kouider, 2017). In a multilevel architecture, computations across all the instances would be an intractable problem. The figure-and-ground analogy suggested by Bernstein (1947) may contain a heuristic solution of the problem. The clue is in reducing a multilevel architecture of immense complexity to a basically two-level virtual construct, as “the minimal architecture of consciousness”, which is much simpler than that of the entire human brain (Kotov, 2017). One finds the largest number of examples for such a reduction of complexity in research on phenomenology of visual perception, from Edgar Rubin's initial observations to seminal experiments of Karl Dunker (1929) on the induced motion effects in the presence of multiple frames of reference. It is too bad that we cannot anymore discuss the validity of such analogies with Bruce Bridgeman – a friend and the great expert in both visual perception and the psychology of consciousness.

5. Conclusions and outlook

The functional imaging revolution in the late 1990s has promoted the view of the brain as being organized into multilevel network architecture. While the nomenclature of large-scale mechanisms in the human brain has since been under intense debate, it is only recently that we have first evidence on hierarchical relations among some of these networks (Zhou et al., 2017). Given this knowledge the purpose of our article was threefold. First, we aimed to describe early research that anticipated the current development in cognitive-affective neuroscience conceptually even if not methodologically. Second, we wished to learn more about causal relations between prefrontal and limbic brain structures. Third and in view of our previous results on asymmetry of connectivity within the DMN (Sharaev et al., 2016; Ushakov et al., 2016), we were interested in testing a possible lateralization of effective connections beyond the DMN core regions. Therefore, masks of symmetrical left and right locations across the brain's midline belonging to three evolutionary different subdivision of the human cortex were selected and submitted to DCM analysis of the regions' connectivity using resting-state data from an fMRI experiment with healthy subjects.

The results of several spectral DCM analyses have demonstrated an impressive rightward bias of excitatory connections between most of the regions selected for our study. Together with the data on the prevalence of self-related contemplation under resting state conditions, this allows us to assume the existence of specific functional mechanisms that we refer to as the “Level of Personal Sense” attributing it to structures of the right hemisphere – neocortex as well as paleocortex and archicortex. Overall the data on lateralization are in agreement with the previously suggested role of the right hippocampal formation as the gateway for processes of self-related cognition, emotional and corporeal awareness (Velichkovsky et al., 2017). Following the proposal by Burgess and Wu (2013), we tentatively attribute the highest level of organization to the function of the FPC and hence refer to it as the “Level of Metacognition”. Unexpectedly we also found multiple causal contributions from the ventrolateral prefrontal-amygdala emotional pathway, specifically VLPCr. We speculate that the role of this structure is so salient in our data because self-related thinking is tightly linked with emotional valuation.

There may be two important heuristics in the functioning of human brain multilevel architecture. One concerns a simple strategy of finding self-related information. As we have argued here and in previous studies, the search can be repeatedly *centered* on representations of *egocentric* space, thereby providing easy-to-find access to most of the information that we call “our subjective experience” (Velichkovsky et al., 2017). The second heuristic can simplify computational problems in a multilevel architecture. We

elaborate here on the figure-and-ground analogy in relationships of the levels (Bernstein, 1947) by filling in the analogy with computational content. The suggested heuristic consists in the architecture's functional reduction to a minimalistic two-level construct. Such a virtual machine has to allow us to simulate imaginary situations, one's own imaginary actions, and imaginary actions of other agents, i.e. to demonstrate features considered essential for reflective consciousness in the philosophy of mind and cognitive psychology. Though it is currently not fully clear how this solution might be implemented, the “source switching” function, central for the FPC (Burgess, Cohen-Yaacovi, & Volle, 2012), can be of significance, for example, by promoting a comparison of objectified (Level E, Conceptual Structures) and personalized (Level F, Personal Sense) views of the same subject-matter. This duplication of content is a necessary step in everyday social interaction, in solving theory-of-mind tasks as well as in understanding metaphorical language, humor, and irony (Bardi, Six, & Brass, 2017; Kotov, 2017; Minsky, 1984).

Our final remark is on the limitations of this study. In part, they reflect the current constrains of research methods. Specifically, it is necessary to develop a DCM methodology for dealing with large and heterogeneous brain structures such as the PFC and the hippocampal formation. Another problem of the method, which constrained the design of our study, is the steep increase of possible models as a function of the number of regions. Modern techniques of large DCM model inversion and comparison (Friston et al., 2016; Litvak, Garrido, Zeidman, & Friston, 2015) can help overcoming the model proliferation issue. Recent progress in significance testing for large directed graphs (Sharaev, Orlov, Ushakov & Velichkovsky, 2018) may also help address this problem. With all the limitations, the current study is the first to demonstrate the lateralization of causal interactions within and between prefrontal and limbic structures during resting state, which is after all the basic state of human consciousness.

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