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New Insights into the Human Brain's Cognitive Organization: Views from the Top, from the Bottom, from the Left and, particularly, from the Right

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Abstract

The view that the left cerebral hemisphere in humans "dominates" over the "subdominant" right hemisphere has been so deeply entrenched in neuropsychology that no amount of evidence seems able to overcome it. In this article, we examine inhibitory cause-and-effect connectivity among human brain structures related to different parts of the triune evolutionary stratification — archicortex, paleocortex and neocortex— in relation to early and late phases of a prolonged resting-state functional magnetic resonance imaging (fMRI) experiment. With respect to the evolutionarily youngest parts of the human cortex, the left and right frontopolar regions, we also provide data on the asymmetries in underlying molecular mechanisms, namely on the differential expression of the protein-coding genes and regulatory microRNA sequences. In both domains of research, our results contradict the established view by demonstrating a pronounced right-to-left vector of causation in the hemispheric interaction at multiple

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levels of brain organization. There may be several not mutually exclusive explanations for the evolutionary significance of this pattern of lateralization. One of the explanations emphasizes the computational advantage of separating the neural substrates for processing novel information ("exploration") mediated predominantly by the right hemisphere, and processing with reliance on established cognitive routines and representations ("exploitation") mediated predominantly by the left hemisphere.

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Keywords: fMRI; effective connectivity; levels of cognitive organization; dynamic causal modeling (DCM); protein-coding genes; microRNA; gene expression; modes of attention; hemispheric lateralization

1. Introduction

The view that the left cerebral hemisphere in humans “dominates” over the “subdominant” right hemisphere has been so strongly embraced in neuropsychology that no amount of evidence seems able to overcome it. At the same time, there is an ever growing number of observations that contradict this entrenched notion. Suggestions of right hemisphere dominance can be found in a variety of domains. For example, behavioral 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 with longer fixations [1],[2],[3]. Subsequent research has demonstrated that this ambient-to-focal shift temporally overlaps with a shift of activity from the right to the left hemisphere demonstrating a rightward dominance in the early phase of visual processing [4],[5].

In the clinical context, disorders of consciousness primarily results from lesions of the right hemisphere [6-8]. We recently described two 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 the left inferior parietal cortex (IPCl) and 58 persons with lesions in the right inferior parietal cortex (IPCr) [9]. Despite individual variability, these patterns were clearly distinct. The IPCl patients tended to overestimate the actual complexity of the surrounding world of things and standard social situations, whereas the IPCr patients were prone to simplifying social interactions as they failed to recognize mental states and to attribute these states to other people. According to neuroimaging studies, the right prefrontal areas are preferentially involved in the retrieval of autobiographical memories, personally-related encoding of information, and planning for the future [10],[11],12], i.e. the processes that are directly related to the conscious «self».

A common assertion is that the left hemisphere is “dominant” because it supports language, or at least most of its aspects. Contemporary neurolinguistic studies show a more complex picture. While the left hemisphere supports basic linguistic functions in the vast majority of humans, the right prefrontal cortex is important for dealing with “language in social context”, i.e. with communication pragmatics, metaphorical and emotional expressions, humor, irony and sarcasm [13],[14]. In a pioneering study of natural speech semantics, Alexander Huth and his colleagues [15] have demonstrated a broad distribution of activities for global semantic dimensions across both hemispheres instead of the expected leftward bias. Moreover, an asymmetry focusing on the right temporoparietal junction was found for categories with “mental”, “emotional”, and “social” attributes.

The study by Huth et al. used a flat projection of categories on the neocortex and it was therefore impossible to determine whether underlying limbic structures were involved. The role of these structures can, however, be substantial as it has been earlier shown in our studies of effective (cause-and-effect) connectivity of the left and right hippocampal formation (HIPl and HIPr, respectively) within the Default Mode Network (DMN) [16]. In these studies, we applied spectral Dynamic Causal Modeling (DCM) to resting-state functional magnetic resonance imaging (fMRI) data. The main purpose of DCM is to evaluate the parameters of a biologically validated model of the neuronal system so that it can predict the observed fMRI data in the best possible way [17],[18]. By using this methodology, we have recently demonstrated a massive right-to-left direction of the excitatory influences under resting state when self-related contemplation prevails over more objectified conceptual thinking [19],[20]. In selecting regions of interest (ROIs) for

these studies, we paid attention to the presence of structures belonging to different levels of brain's evolutionary architecture [8],[21]. The anterior neocortex was represented by the left and right frontopolar cortices (or, in earlier notation, by FPCl and FPCr), ventrolateral prefrontal cortexes (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.

In a parallel line of research on underlying molecular mechanisms, our group has revealed 61 protein-coding genes differentially expressed between FPCr and FPCl [22]. Significantly more genes were up-expressed in the right hemisphere than in the left (40 to 21, respectively). In aiming to explain these results, we used the ROBBIA (ROtman-Baycrest Battery to Investigate Attention) neuropsychological model, which proposes a prefrontal specialization of two distinct cognitive functions [23],[24]. One is the right-lateralized monitoring function providing cognitive resources to maintain abstract representations by monitoring their status in relation to each other and to intended behavior. The other specialization is left-lateralized task-setting function, defined as the transient cognitive control needed to form task-relevant rules and suppress task-irrelevant operations.

More or less implicit in the ROBBIA model is a presumption about inhibitory operation mode of the left hemisphere contrasting to excitatory character of the right-to-left connections. As far as we know, the hypothesis was never directly tested, neither in the effective connectivity studies nor in investigations of brain's molecular mechanisms. In the latter case, a plausible sign of enhanced inhibitory control can be seen in a relative abundance of the up-expressed microRNA sequences. These molecules usually play the role of suppressors to the protein-coding genes (mRNAs). The purpose of our study was to close the gap in knowledge, firstly, by analyzing possible presence of a significant left-to-right inhibitory causation in our fMRI data, and, secondly, by testing the differential expression of microRNA in the left and the right hemispheres in the available sample of human brain. The methods and results of these two components of our study are presented separately below.

2. Study 1: Is there a significant left-to-right inhibitory connectivity under resting state?

2.1. Material and Methods

2.1.1. 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 to 35 years). Informed consent was obtained from each participant. All participants were asked to maintain wakefulness with closed eyes 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 local Ethics Committee of the National Research Center "Kurchatov institute" (Protocol No.10 from the 1st of August 2018).

2.1.2. Scanning parameters

Since spectral DCM (root) mean square error decreases as the number of time points increases [25] we decided to acquire 1000 time points (with a repetition time of 2s) resulting in approximately 35 minutes 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 mm^2. 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 mm^2.

2.1.3. 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 [26]. Next, slice-timing correction for fMRI data was performed (the correction of the hemodynamic response in space and then in time to avoid pronounced motion artifacts; [27]. 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.

Further details of the method and measurement instruments can be found in our previous publication [19]. 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 [28], 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 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 [18].

The obtained SPMs were then masked with previously created masks for FPCl/r, VLPCl/r, IPCl/r, AMYl/r, and HIPl/r. Next, the intersection of mask and SPM 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 [16], the principal eigenvariates of the time-series were extracted from spheres (8 mm radius) centered at the appropriate Montreal Neurological Institute (MNI) coordinates of the respective brain's regions. These coordinates are presented in the table 1. For FPC and VLPC the principal eigenvalues of time-series were extracted without the sphere assignment, on the basis of BOLD signal fluctuation over entire Brodmann areas.

Table 1. MNI coordinates for the centers of selected ROI masks. Time-series for both FPC and VLPC were extracted from appropriately masked SPMs without additional sphere assignment, i.e. the principal eigenvariates were extracted from entire Brodmann areas.

Left Hemisphere	HIPl	AMYl	IPCl	VLPCl	FPCl
MNI coordinates or Brodmann Areas (BA)	-22, -23, -14	-22, -4, -18	−50, −3, 32	(BA44, 45, 47)	(BA10)
Right Hemisphere	HIPl	AMYl	IPCl	VLPCl	FPCl
MNI coordinates or Brodmann Areas (BA)	22, -23, -14	22, -4, -18	48, −69, 35	(BA44, 45, 47)	(BA10)

For the purpose of this follow-up investigation, we performed one additional statistical analyses separately for connections that demonstrate influence of left hemisphere structures on the right ones (L>R) and vice versa (R>L). In particular, we compared these data within the 5 pairs of symmetrically located ROIs for the scans 1 to 500 (approximately first 15 minutes) and the scans 501 to 1000 (approximately last 15 minutes) of the experiment. Such a separate consideration was caused by earlier reports that the very novelty of scanning situation for participants may influence the size and the direction of lateralization effects [29]. Simple statistical procedures were selected, which was the one-sample t-test with Bonferroni correction.

2.2. Results

The results of our analysis are presented in the table 2. They show a rather clear picture of relations. First of all, a strong dominance of the R>L influences ($p < 0.01$) was discovered in all ROI pairs −except posterior neocortical areas IPCl/r mutually influencing each other− at the beginning (scans 1 to 500) and at the end (scans 501 to 1000) of the experimental session. The influence of effective connections in the opposite direction, L>R, remained non-significant for all pairs of locations, with the only exception of the left and right frontopolar cortex, where only just significant ($p < 0.049$) excitatory influence was found in the second half of the experiment. No statistically significant (or even approaching statistic significance) left-to-right or right-to-left inhibitory influence was found in any of symmetrically located pairs of ROIs.

Table 2. Group mean connection strengths for the first and second half of the experiment[1]. Top rows for connections with left to right causation, bottom – right to left causation. SDs are in brackets. Nontrivial significant connections survived the Bonferroni correction are marked with * ($p < 0.05$), ** ($p < 0.01$).

	HIPl/r	AMYl/r	IPCl/r	VLPCl/r	FPCl/r
			Left to Right		
1-500	-0.03(0.32)	0.01(0.39)	0.18(0.35)*	0.00(0.57)	0.10(0.37)
501-1000	0.02(0.33)	0.05(0.33)	0.18(0.33)*	-0.09(0.54)	0.16(0.37)*
			Right to Left		
1-500	0.41(0.47)**	0.27(0.44)**	0.29(0.38)**	0.57(0.42)**	0.32(0.40)**
501-1000	0.47(0.51)**	0.28(0.40)**	0.24(0.41)**	0.54(0.40)**	0.27(0.38)**

[1]Individual data of connection strengths for all 25 subjects of this study can be received from the first author on request.

3. Study 2: Is there a prevalence of microRNA expression in the left frontopolar cortex?

3.1. Material and Methods

3.1.1. Human brain tissue

Postmortem samples of human brain tissue from the left and right FPC areas from ten donors were obtained using the resources of three institutions: Partner Institute of Computational Biology of Chinese Academy of Sciences, Max Planck Institute for Evolutionary Anthropology and NIH NeuroBioBank. This sampling consisted of six BA10L samples and four BA10R samples from male/female individuals without a known history of psychiatric and neurological diseases. Mean age 39.79±3.23 years old, mean postmortem interval 12.10±1.76 h (mean±SD). Permission to undertake this study was granted by the local was granted by the local Ethics Committee of the National Research Center “Kurchatov institute” (Protocol No.10 from the 1st of August 2018).

3.1.2. RNA extraction

Isolation of total RNA from brain tissue samples was carried out using Trizol reagent (Thermo Fisher Scientific, USA) according to the manufacturer's instructions. RNA concentration was determined by fluorimeter Qubit 2.0 using Qubit RNA HS Assay Kit (Thermo Fisher Scientific, USA). RNA integrity number (RIN) was assessed by BioAnalyzer 2100 (Agilent Technologies, USA) and RNA 6000 Nano kit (Agilent Technologies, USA). The RIN ranged from 6.1 to 9.3 for all samples.

3.1.3. Library preparation and sequencing

10 microRNA libraries for sequencing were constructed using 0,7-1 μg of total RNA per sample and the NEBNext Multiplex Small RNA Library Prep Set for Illumina Set 1 (New England Biolabs, USA) according to the manufacturer's instructions. The final library met all quality metrics as defined by Illumina, and library quantitation was performed on an Agilent 2100 Bioanalyzer with a High-Sensitivity DNA kit (Agilent Technologies, USA) prior to sequencing. MicroRNA libraries were sequenced using an Illumina HiSeq 1500 platform (Illumina, USA) with 50-bp single-end reads.

3.1.4. Sequencing analysis

After quality (Q20) and adapter trimming using cutadapt 2.0 (Martin, 2012) DNA-reads were mapped to the reference human genome (hg19) using bowtie2 [30], with default options. The resulting SAM file was converted to a BAM file with SAMtools v.1.4 (http://samtools.sourceforge.net/), then transformed into a BED, from which the depth

of each microRNA was derived using the coverageBed tool based on the human microRNA annotation from miRBase v.21 [31]. The differential mature microRNA expression between BA10L and BA10R were analyzed using the RNA protocol of DESeq2 software (Love et al., 2014) in R (https://www.r-project.org/) programming environment as well as PCA analysis. MicroRNA target prediction was performed using the online database miRDB (Wong and Wang, 2015)

3.2. Results

The total number of microRNA raw reads generated for both FPCl and FPCr areas was from 5 to 10.4 million sequences per sample (data are deposited at NCBI Bioproject: PRJNA388140). At least 92% of reads were map d to the reference genome. To compare FPCl and FPCr microRNA profiles, we used only the most reliable microRNAs. The compositional profiling revealed that the most abundant in left and right FPC libraries was the 23-nt fraction. In view of the large quantity of results that need to be presented in a special publication, we consider below only those data that are relevant to answering main questions of this study.

The vast majority of identified microRNAs did not differ in expression between FPCl and FPCr areas demonstrating that both distributions are very similar and highly heterogeneous. Due to these features, a statistically significant differential expression in microRNAs between the left and right FPC samples was found only for minority of them. All in all, the comparative study of the microRNA expression in the right and left areas of FPC allowed us to identify 7 microRNAs significantly up-expressed in FPCl whereas 17 microRNA genes were up-expressed in FPCr. All statistically significant cases of such differential expression are listed in tables 3 and 4.

Table 3. Mature microRNAs molecules, which are up-expressed in left FPC.

Gene ID	Gene name	log2 (Fold Change)	p-value
MIMAT0018191	*hsa-miR-3917*	0.6015	0.0446
MIMAT0003180	*hsa-miR-487b-3p*	0.3254	0.0437
MIMAT0022705	*hsa-miR-539-3p*	0.5427	0.0122
MIMAT0022844	*hsa-miR-216a-3p*	0.5964	0.0347
MIMAT0003242	*hsa-miR-577*	0.8851	0.0054
MIMAT0027032	*hsa-miR-500b-3p*	0.6922	0.0310
MIMAT0001545_1	*hsa-miR-450a-5p*	0.5157	0.0376

Table 4. Mature microRNAs molecules, which are up-expressed in right FPC.

Gene ID	Gene name	log2 (Fold Change)	p-value
MIMAT0000266	*hsa-miR-205-5p*	0.7409	0.0230
MIMAT0005949	*hsa-miR-664a-3p*	0.6088	0.0161
MIMAT0005792_1	*hsa-miR-320b*	0.6473	0.0242
MIMAT0002890	*hsa-miR-299-5p*	0.4991	0.0074
MIMAT0022862	*hsa-miR-381-5p*	0.8278	0.0110
MIMAT0019814	*hsa-miR-203b-3p*	0.6667	0.0394
MIMAT0004614	*hsa-miR-193a-5p*	0.5244	0.0281
MIMAT0005793_1	*hsa-miR-320c*	0.6508	0.0197
MIMAT0003311	*hsa-miR-641*	0.7720	0.0147
MIMAT0005577	*hsa-miR-1226-3p*	0.5688	0.0256
MIMAT0000437	*hsa-miR-145-5p*	0.6040	0.0416
MIMAT0022472	*hsa-miR-5683*	0.8631	0.0058
MIMAT0018926_1	*hsa-miR-378d*	0.8729	0.0052

MIMAT0005887	*hsa-miR-1299*	0.7329	0.0246
MIMAT0000705	*hsa-miR-362-5p*	0.6074	0.0072
MIMAT0000280	*hsa-miR-223-3p*	0.7376	0.0029
MIMAT0006764_1	*hsa-miR-320d*	0.8508	0.0063

A number of these microRNAs were already described as brain-specific – *hsa-miR-299-5p*, *hsa-miR-487b-3p*, and *hsa-miR-539-3p* [32],[33] or known as mental disorder-related molecules – in left FPC: *hsa-miR-500-3p* [34]; in right FPC: *hsa-miR-193a-5p* [35], *hsa-miR-203-3p* [36], *hsa-miR-205-5p* [37,38], *hsa-miR-223-3p* [39,40], *hsa-mir-299-5p* [41], *hsa-mir-320b*, *hsa-mir-320c*, *hsa-mir-320d* [34,39], *hsa-miR-362-5p* [38], and *hsa-miR-664a-3p* [34].

Target site prediction analysis for these microRNAs and protein-coding genes described by our group previously [22] showed that several of microRNAs possibly down-regulates protein-coding genes related to brain development and mental conditions (Figure 1, Supplementary Tables 1-2). For example, *hsa-miR-205-5p* that distinguished Parkinson disease [37], [38] has three mRNA targets – Rho GTPase activating protein 24 (ARHGAP24), rubicon autophagy regulator (RUBCN), zinc finger and BTB domain containing protein 20 (ZBTB20). Of interest is the ZBTB20 gene because it modulates the sequential unfolding of neuronal layers [42] and promotes astrocytogenesis during brain development [43]. ZBTB20 also plays an essential role in the specification of the Cornu Ammonis-1 field identity in the developing hippocampus, a region implicated in major depression [44] and seasonal affective disorders [45]. This gene is apparently repressed by five different microRNAs, which according to our results are all up-expressed in the right FPC: *miR-145-5p*, *hsa-miR-205-5p*, *hsa-miR-378d*, *hsa-miR-1299*, and *hsa-miR-5683*.

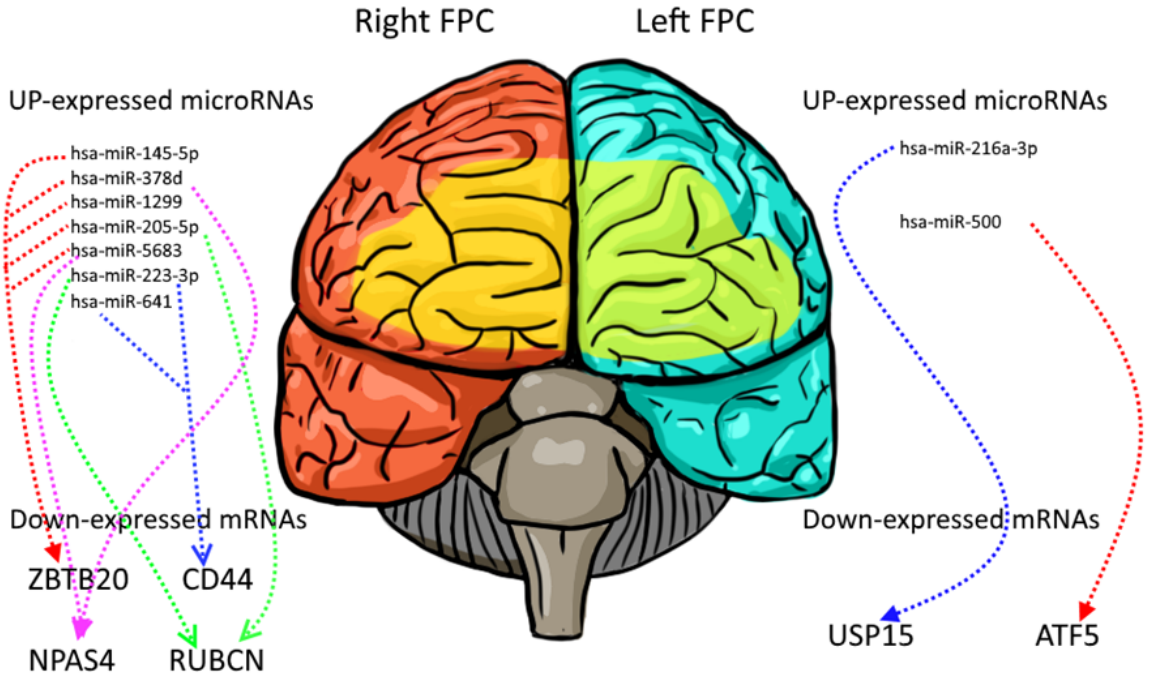

Fig. 1. Main possible mRNA targets of differentially expressed microRNA in left and right FPC.

4. General Discussion

The results of reported studies give negative answers to both main research questions of this work. We found neither significant left-to-right inhibitory connections under resting state nor a prevalence of microRNA expression in the left frontopolar cortex in comparison to the rught. If one needs further evidence to already listed examples of right-to-left dominance in the brain functional architecture, this evidence is provided by our data. Does it means demise for the particular model of prefrontal hemispheric specialization; the ROBBIA model? This is not a necessary conclusion,

because the model was developed to deals with task-positive processing while our data on asymmetries in patterns of effective connectivity were obtained in task-negative resting state conditions. However, our results provide arguments against an overgeneralization of the model's validity. Any neuropsychological model can be considered as complete only if it includes description of brain processes at rest. In fact, resting states only seems to be "task-negative". Recent research revealed their crucial importance as periods of elaborated brain activity making introspection, social cognition, reflective thinking, and creative problem solving possible [46], [47].

Studies of lateralization at large-scale and at molecular levels are of practical significance for medicine: cognitive disorders and psychiatric diseases such as schizophrenia, autism, and dyslexia are accompanied by disturbances in brain asymmetry [48], [49], [50], [51]. Literature search of reported microRNAs with differential frontopolar expression resulted in the detection of 12 out of 24 microRNAs implicated in schizophrenia. For example, those are *hsa-miR-145-5p* [52]; *miR-360* with family representatives *hsa-miR-320b*, *hsa-miR-320c*, *hsa-miR-320d* [53]; hsa-*miR-223-3p* [54]. The finding aligns well with the data from our study of protein-coding [22], where about a half of genes with lateralized expression in PFC were related to schizophrenia. The vast majority of these genes (~67%) were up-expressed in PFCr. No such wide association with other mental disorders was found. Thus, it can be assumed that FPC has a key involvement in this disease.

From the perspective of basic research, we have to note an affinity of data about effective connectivity of FPC and the hippocampal formation, on the one hand, and similarity of their molecular mechanisms expressed at both these levels of brain evolutionary organization, on the other. We earlier reported that genes, which are strongly up-regulated in the right FPC, namely *C-FOS*, *NPAS4*, *SERPINA3* and *mir-331*, also are known for their role in molecular mechanisms of the hippocampal formation [22]. The same conclusion can be made from results of this study related to *ZBTB20* gene, which is under influence of 5 microRNA suppressors up-expressed in the right PFC but seems to have major functions in the developing hippocampus as well. An interaction of VLPC with amygdalae is similarly of importance for emotional reaction to stressful situation including the MRI experiments [20]. In other words, the answer on many research questions of cognitive neuroscience can be found only in the analysis of interaction between upper and lower-level structures of brain's evolutionary hierarchy.

The reference to evolution helps to understand why the left hemispheric dominance for language cannot fully capture the nature of hemispheric specialization: language is a very late evolutionary achievement, whereas hemispheric specialization is a pervasive feature of, at least, mammalian evolution [46]. There are several alternatives. One possible explanation involves the evolutionary significance of two reciprocal modes of attention. The focal mode of attention is fine-grained and focused on object recognition, the other, ambient mode is distributed across the environment at large and serves spatial orientation, watching out for dangers, and interpreting intentions of social counterparts [20], [55]. Another hypothesis emphasizes the evolutionary significance and computational advantage of separating the neural substrates for processing novel information ("exploration") mediated predominantly by the right hemisphere, and processing with reliance on established cognitive routines and representations ("exploitation") mediated predominantly by the left hemisphere [46]. The third, not mutually exclusive explanation stresses the role of self-referential cognitive-affective processes, which may be biased by the asymmetries in egocentric spatial representation at the level of archicortex, namely the hippocampal formation [16], [19].

5. Conclusions

The novelty of our findings lies, firstly, in the fact that we examined causal relations between multiple brain regions using resting fMRI. Although reported results are based on a rather limited set of experimental data in terms of the number of subjects or in terms of the number of available samples of human brains, they provide a clear evidence against the established view on the left hemisphere dominance in human brain activity. The right-to-left causation seems to be a general case because it has its evolutionary roots in interaction between several levels of brain organization and is typical for resting state, i.e. for the baseline state of human consciousness. Secondly, our results on differential microRNA expression together with previously published data about expression of protein-coding genes at the very top of human brain's evolutionary hierarchy, FPC, testify to more active and elaborated molecular processes in the right FPC. Despite these new data on lateralization of microRNA in the youngest regions of the human cortex, the research domain of the working brain molecular machinery remains largely underexplored. As a whole, this is probably the next "terra incognita" of cognitive neuroscience.

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