Brain functional organization and structure in patients with arteriovenous malformations

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Abstract

Purpose Developmental in nature, brain arteriovenous malformations (AVM) have the potential to affect whole brain organization. Here we investigated the impact of AVM on functional and structural brain organization using resting-state functional MRI (rsfMRI) and cortical thickness measures.

Methods We investigated brain functional organization and structure using rsfMRI in conjunction with cortical thickness analyses in 23 patients with cerebral arteriovenous malformations (AVMs) and 20 healthy control subjects.

Results Healthy controls showed the expected anti-correlation between activity in the default mode network (DMN) and frontal areas that are part of the attentional control network. By contrast, patients demonstrated a disruption of this anti-correlation. Disruptions to this anti-correlation were even observed in a subgroup of patients with lesions remote from the main nodes of the DMN and were unrelated to differences in perfusion. Functional connectivity differences were accompanied by reduced cortical thickness in frontal attentional areas in patients compared to the controls.

Conclusions These results contribute to the discussion that AVMs affect whole brain networks and not simply the area surrounding the lesion.

Keywords Arteriovenous malformations · Resting state networks · Cortical thickness · Brain development

Introduction

Brain arteriovenous malformations (AVMs) are lesions of the vascular system involving direct connection between arteries and veins without an interposing capillary bed [1]. The etiology and natural history of AVMs is unclear. While AVMs have been regarded as congenital lesions resulting from errors in embryonic vascular morphogenesis, there is increasing evidence that they may also develop after birth and continue to be modified by environmental factors and aberrant gene expression throughout the lifespan [1, 2]. AVMs often only become symptomatic in adulthood with the most common presenting symptoms being seizures or intra-cerebral hemorrhage [3, 4]. A small subset of patients, 7–15% depending on the study, will present with focal neurological deficits [5]. Many patients with AVMs remain asymptomatic and their lesions are only discovered incidentally [6].

The developmental nature of AVMs, and their formation during critical periods of brain development, as well as previous evidence that points to functional plasticity in patients, has led to the question of the potential effects of AVMs on whole brain organization and structure [7, 8]. A promising method for investigating this question is resting-state functional MRI (rsfMRI). Coherent low-frequency fluctuations in blood oxygen level–dependent (BOLD) signal when an individual is in a state of wakeful rest are thought to reflect the brain’s intrinsic functional organization [9, 10]. Correlations in the
spontaneous BOLD signal between different brain regions allow for the delineation of functional networks [9, 11].

In the present study, we aimed to investigate resting state connectivity in patients with AVMs compared to a group of healthy control subjects with a focus on the default mode network (DMN) and its anti-correlation with the attentional network. DMN consists of a set of brain regions that are engaged when an individual is not involved in a task requiring external attention. This network includes the posterior cingulate cortex, the medial prefrontal cortex, and the lateral parietal cortex [9]. The activity in this network is generally found, in healthy subjects, to be anti-correlated with a task-positive network consisting of regions in the intraparietal sulcus and inferior parietal lobe, pre-central sulcus, dorsolateral prefrontal cortex, insula/frontal operculum, and the supplementary motor area that are engaged in tasks requiring external attention [11]. Abnormalities in the DMN and its anti-correlation with the task-positive network have been observed in several psychiatric and neurological disorders including schizophrenia, attention deficit hyperactivity disorder, and even in normal aging [12–16]. Rudimentary versions of these networks exist from early infancy and continue to develop until early-adulthood potentially coinciding with the developmental trajectory of AVMs [17, 18]. Because of the potential of AVMs to cause abnormalities in the BOLD signal [7], we performed an additional perfusion analysis using pseudo-continuous arterial spin labeling (PCASL) to confirm that resting state findings were not artifacts of abnormal perfusion. We also sought to supplement the resting-state connectivity analysis with an anatomical analysis of cortical thickness to assess whether functional connectivity differences were accompanied by thinning or thickening of the cortex.

Methods

Participants

The sample was comprised of 23 consecutive patients with brain AVMs (11 females, average age of 33 years) and 20 healthy control subjects (7 females, average age 30 years) that were matched for age \((t = 1.076, df = 41, p = 0.288)\) and sex. (Demographic and clinical information for the patients is provided in Table 1).

The diagnosis of AVM was made at the Department of Neuroradiology of the Montreal Neurological Hospital by neuroradiologists with specific expertise in cerebrovascular disorders and endovascular intervention. Diagnosis was based on brain MRI obtained in the clinical setting and confirmed with conventional angiogram. Based on clinical exam, all patients included in the study were also determined to be without a major cognitive deficit. Patients with previous surgical, radiosurgical, or endovascular treatment and those with a history of intracerebral hemorrhage were not included in the study.

We first performed the analyses on the whole patient group whose lesions are depicted in Fig. 1a. Due to the prominence of the frontal and parietal regions in the DMN [9] and the potential for hemodynamic confounds in interpreting resting state results in patients with AVM lesions in the fronto-parietal network, we then performed a second analysis on a subset of 12 patients with non-fronto/parietal lesions which are depicted in Fig. 1b [19].

MRI data acquisition

The imaging data was acquired on a 3T Siemens TrioTim scanner using a 12-channel head coil at the McConnell Brain Imaging Centre of the Montreal Neurological Institute. T1-weighted images were acquired using a 3D magnetization-prepared rapid gradient echo (MP-RAGE) sequence (slice thickness = 1 mm, TR = 2300 ms, TE = 2.98 ms, matrix size = 256 × 256, FoV = 256 mm, flip angle = 9 deg., interleaved excitation). Resting state images were acquired with a 2D EPI (echo planar imaging sequence) with 42 3.5-mm-thick transverse slices covering the whole brain (TR = 2210 ms, TE = 30 ms, matrix size = 64 × 64, FoV = 224 mm, flip angle = 90 deg); 136 volumes were acquired. Perfusion data was acquired in a subset of the patient sample \((n = 11)\) with PCASL (TR = 4000 ms, TE = 9.9 ms, voxel size = 3.5 × 3.5 × 6.0 mm, label duration = 1.48 s, post-label delay = 1.2 s). A separate equilibrium magnetization map (M0 scan) without labeling was also obtained with the same parameters (TR = 15,000 ms) in order to estimate cerebral blood flow (CBF). Imaging data was acquired over an extended time frame, and the PCASL was only included towards the end of data collection.

Resting-state fMRI analysis

Resting-state fMRI data were first preprocessed using SPM8 using standard preprocessing steps including slice timing correction, realignment, coregistration to structural image, normalization, and smoothing with a 6-mm full width at half maximum (FWHM) Gaussian kernel [20]. Motion outliers were identified using ART (Artifact Detection Tools), and removed from the analysis. Outliers were defined as volumes in which head movement exceeded 1 mm from the previous volume or volumes in which the average intensity was more than 3 standard deviations from the mean intensity of the session.

Seed-based resting-state connectivity analyses were performed using the Matlab/SPM based CONN toolbox [20]. We performed our analysis by estimating the temporal correlation between the BOLD signal in our seed and the rest of the brain. We selected a seed in the ventro-medial prefrontal cortex corresponding to one of the primary nodes of the DMN. This was defined as a 10-mm sphere at MNI coordinates (−1, 0, 0).
To produce first-level correlation maps, the BOLD time course from this seed region was extracted, and Pearson’s correlation coefficients were calculated between this and that of all other brain voxels. These correlation coefficients were converted to normally distributed $Z$ scores using a Fisher transformation in order to allow for second-level analyses. All reported clusters survived an FWE-corrected threshold of $p < 0.01$ and an uncorrected voxel-level threshold of $p < 0.001$, two sided.

Following the suggestion that the SD of the time series is reflective of cerebrovascular reactivity [21] and in order to probe the reliability of using BOLD-derived functional connectivity metrics in a patient population with vascular malformations such as in our sample, we examined the overall standard deviation (SD) of the denoised BOLD time series in masks of non-lesion areas of the patients and in the whole brain in controls. We used an $F$ test to compare the standard deviation of the BOLD time series between patients and controls.

Cortical thickness analysis

Cortical reconstruction and volumetric segmentation were performed using Freesurfer imaging suite (http://surfer.nmr.mgh.harvard.edu/). These procedures have been described in detail in prior publications [22-24]. Processing includes motion correction and averaging of volumetric T1 images [24], removal of non-brain tissue, Talairach transformation, intensity normalization [25], tessellation of the gray/white matter boundary, automated topology correction [26], and surface deformation following intensity gradients to optimize placement of gray/white matter and gray/cerebrospinal fluid (CSF) boundaries at the location where the greatest intensity shift defines the transition to the other tissue class [22, 23]. The cortical surface was parcellated into 34 regions using the Desikan atlas implemented in Freesurfer [27]. Cortical thickness was calculated as the closest distance from the gray/white matter boundary to the gray matter/CSF boundary at each vertex of the tessellated surface [23]. Data maps were smoothed with a 20-mm FWHM Gaussian kernel. Because of the potential for cortical AVMs to interfere with the cortical reconstruction, we chose not to perform a whole brain analysis, instead the focus was on specific brain regions which were remote from the lesions of our AVM group.

Average cortical thickness within regions of interest in the left and right dorsolateral prefrontal cortex was extracted and an independent samples $t$ test was conducted to compare cortical thickness in these regions between the patients with non-frontal/parietal lesions and the control group. Using Pearson’s correlations, we also evaluated the relationship between the resting-state connectivity findings and cortical thickness within these ROIs [28].

Perfusion analysis

A perfusion analysis was conducted to control for potential effects of perfusion on resting state connectivity. Data were processed using ASLtbx [29] with SPM8. Labeled and unlabeled arterial spin labelling (ASL) images were
independently motion corrected and then a combined mean image was created which was then coregistered to the T1-weighted image. The ASL images were then resliced to match the mean image and spatially smoothed with a 6-mm FWHM Gaussian kernel. Cerebral blood flow (CBF) was estimated by subtraction resulting in a mean CBF image. CBF calibration (to yield perfusion maps in ml/100 g/min) was conducted using the following equation:

\[
f = \frac{\Delta M \lambda R_{1a} \exp(\omega R_{1a})}{2M_0 \alpha \left[1 - \exp(-\tau R_{1a})\right]}^{-1}
\]

where \( f \) is CBF, \( \Delta M \) is the signal difference between control and label images, \( R_{1a} \) is the longitudinal relaxation rate of blood, \( \tau \) is the labeling time, \( \omega \) is the post-label delay time, \( \alpha \) is the labeling efficiency, \( \lambda \) is blood/tissue water partition coefficient, and \( M_0 \) is approximated by the control image intensity [29]. The parameters used in this study were as follows: \( R_{1a} = 0.67 \, \text{s}^{-1} \), \( \tau = 1480 \, \text{mms} \), \( \omega = 1200 \, \text{ms} \), \( \alpha = 0.85 \), \( \lambda = 0.9 \, \text{g/ml} \). The T1-weighted image was then normalized using SPM8’s unified segmentation-normalization and these parameters were used to reslice the CBF and T1 images to standard space. Resultant CBF images were then masked with SPM8’s default brain mask in order to remove non-brain voxels. Average perfusion values within masks of bilateral frontal lobes were then extracted for each of the participants. We used frontal lobes as masks because they contain both the primary node of the DMN (the medial prefrontal cortex) and the region of the DLPFC implicated in the attentional network.

Fig. 1 Lesion spatial probability map for the whole patient group (a) and patients with lesions outside of the frontal and parietal lobes (b). Lesion boundaries were first manually delineated, and the resultant lesion masks were then averaged and overlaid on a template volume.
Results

Group differences in functional connectivity between the patients and the control group

Compared to the control group (Fig. 2a), the patients (Fig. 2b) showed diminished anti-correlation between the mPFC seed and bilateral dorsolateral prefrontal cortex, bilateral superior lateral occipital cortex, left middle and inferior temporal gyrus, and right supramarginal gyrus. Controls showed stronger connectivity between this seed and a cluster comprising hippocampus, parahippocampal gyrus, and thalamus as well as bilateral dorsal prefrontal cortex as well as anterior cingulate and left pre-central gyrus. Connectivity from mPFC to left DLPFC was correlated with lesion size ($r = 0.404$, $p = 0.56$) but this did not reach significance.

The subset of patients with non-frontoparietal lesions (Fig. 2c) showed a similar pattern as the whole patient group: an attenuated anti-correlation between activity in the mPFC seed and areas in the bilateral dorsolateral prefrontal cortex (DLPFC), superior lateral occipital lobes, and left middle temporal gyrus. The control group showed a stronger connection between this seed and a cluster comprising the hippocampus, parahippocampal gyrus, and thalamus.

Group differences in BOLD time-course variation

There were no significant differences in the standard deviation of the BOLD time course between non-lesion areas of the patients and controls $F = 1.32$, $p = 0.55$.

Cortical thickness in dorsolateral prefrontal cortex in patients with non-fronto/parietal lesions

We observed reduced cortical thickness in the patients with non-fronto/parietal lesions compared to controls in the left and right DLPFC ($t = 2.56$, $df = 30$, $p = 0.016$ and $t = 2.84$, $df = 30$, $p = 0.008$ respectively). Thickness in the left DLPFC

Fig. 2 Resting state connectivity between mPFC seed and the rest of the brain in controls (a), AVM patients (b), and the subset of patients with non-fronto-parietal lesions (c). Orange/red clusters are regions where activity is positively correlated with the seed region; purple/pink clusters show regions where activity is anti-correlated with the seed region. Above is a volumetric representation of the resting state connectivity, below a surface projection of the same data
correlated with functional connectivity between the mPFC and this region with patients with thicker cortex showing higher degree of anti-correlation but this relationship did not reach statistical significance \( r = -0.506, p = 0.093 \).

**Relationship between functional connectivity and cerebral blood flow**

We found no relationship between cerebral blood flow (CBF) within the left and right frontal lobes and the resting state connectivity between the mPFC and left and right DLPFC of the patients with non fronto-parietal lesions \( (r = 0.138, p = 0.768, \text{and } r = -0.172, p = 0.712) \).

**Discussion**

Patients harboring AVMs historically have been considered to have a localized disease, but more recent studies with single cases have suggested the possibility that AVMs might have a more global impact on brain organization \([8, 30]\). In the present study, with a large cohort of patients, our results add evidence for a global impact on brain functional organization. This was the case when the whole group of AVM patients was examined, and was also evident even in a subgroup of patients where the AVM fell outside the affected network. The presence of an AVM interfered with the anti-correlation known to occur between the DMN and attention network.

The absence of DMN anti-correlation observed in our group of AVM patients with lesions outside of the frontal and parietal lobes (where the most prominent nodes of the attention and default mode networks are located) supports the hypothesis that AVMs affect the whole brain rather than a localized region. Despite the small sample size of this sub-analysis, we found the same pattern of disrupted DMN anticorrelations as in the larger dataset. It is unlikely that the AVM in this subset of patients disrupted the connections in the DMN and between the mPFC seed and the DLPFC regions since the lesions were located outside of the fronto-parietal areas. Of interest, those subjects with thinner cortex in a region of the DLPFC showed a smaller degree of anti-correlation between this region and the mPFC, suggesting that both brain function and structure are affected in regions distant from the AVM. Combining information from resting state connectivity and cortical thickness, our results suggest that both structure and function are impacted by the presence of an AVM. Further studies with larger sample sizes are needed to confirm our findings and analyses of other brain networks will also contribute to our understanding of this phenomenon.

Connectivity results in the subgroup of patients with lesions outside the fronto-parietal region were found to be unrelated to cerebral blood flow, suggesting that the lack of observed anti-correlation was not due to hemodynamic abnormalities. The steal phenomenon is sometimes invoked to explain neurological deficits observed in AVM patients but it does not satisfactorily account for our observations. The fact that we observed disruptions in functional connectivity and cortical thickness in regions remote (contralateral) from the site of the lesion as well as the lack of observed relationship between perfusion and functional connectivity suggests that a current steal phenomenon is not underlying these results. We also did not find any differences in the overall variation BOLD time course between non-lesion areas of the patient sample and controls, suggesting that disruptions of cerebrovascular reactivity caused by AVMs may be limited to the vicinity of the lesion. That said, further exploration with more direct methods for quantifying cerebrovascular reactivity is necessary if we are to establish whether BOLD can be used reliably in this population.

A number of resting-state fMRI studies have demonstrated that the extent of the anti-correlation between DMN and attention networks is predictive of performance on tasks of working memory and attention \([14, 31]\). In a task-based fMRI paradigm, Weissman and colleagues \([32]\) found attentional lapses to be related to a reduced deactivation of the default mode network. Attenuated anti-correlation between default mode network and DLPFC has been implicated in a wide range of conditions characterized by decreased activation in attention and executive function: Keller and colleagues \([14]\) found an absence of MPFC-DLPFC anticorrelations in older adults accompanied by a reduced working memory capacity in this group. Patients with bipolar disorder and schizophrenia were also demonstrated to lack the anti-correlation between MPFC and DLPFC \([12, 15]\). In light of this research, the implication of our resting-state connectivity result is that patients with AVMs could exhibit deficits in attention and executive function. Chai and colleagues \([15]\) found the strength of anti-correlation between DMN and attention networks to increase between ages 8 and 24, possibly reflecting the maturation of these systems. It is possible that the maturation of DMN anticorrelations in the brain coincides with and is influenced by the maturation of AVMs.

Although cognitive function was not tested directly in our sample, anecdotally, many of our patients with AVMs report a lower level of functioning and occupational achievement than comparable groups of patients with non-developmental lesions (i.e., tumors). To date, there is limited discussion on the role attention and executive functions may play in patients with AVMs. The discussion is complicated by the fact that many of the studies investigating this question come in patients with ruptured and unruptured lesions, as well as patients who have undergone treatment. Some evidence suggests potential for cognitive impairments in AVM patients. Steinworth and colleagues observed significant improvements in general intelligence, memory, and attention after radiotherapy, with no differences between patients with and without prior
intracranial hemorrhage [33]. Lazar reported that AVM patients were more likely than the comparison group (intra-cerebral aneurysms and low-grade tumors) to report a developmental learning disorder in school-age years, regardless of lesion size or occurrence of hemorrhage in adulthood [34]. Taken together, these papers also suggest non-localized effects of AVMs on brain function.

While we demonstrated an absence of the anti-correlation between resting state DMN and attentional networks accompanied by differences in brain structure, we did not relate this directly to behavioral performance. The lack of behavioral correlates to our imaging findings is the greatest limitation of the study. It is important to mention that this study was performed retrospectively. It is standard procedure at our hospital for AVM patients to be referred for this functional imaging protocol, but they are only referred for neuropsychological evaluation if they present with obvious impairments or specific complaints. In order to understand the implications of the resting-state connectivity result, a future direction will be to administer neuropsychological assessment to all patients who present with AVMs, regardless of whether they display a clinically evident impairment.

Our study demonstrates the possibility of a global disruption in brain organization in this patient group, and emphasizes the importance of further research. These preliminary findings may have important implications for the clinical management of AVM patients in that we recommend that patients undergo a thorough neuropsychological assessment, in order to document any deficit that may reflect our data. The treatment decision for AVM is based on specific criteria, such as the risk of bleeding and the presence of progressive neurological deficits. In this context, the presence of neuropsychological deficits should be taken into account, but, given the non-negligible risks related to intervention, it is unlikely that they alone will modify treatment indications.

Conclusion

We have demonstrated that patients with AVMs, traditionally considered to be localized lesions, show a wide scale disruption in brain organization as reflected by the resting-state functional connectivity pattern. Patients showed an attenuation of the anti-correlation that is normally present between brain areas involved in attention and the default mode network. This result was apparent even when we looked at patients with lesions distant from the main nodes of the DMN. Connectivity differences were accompanied by reduced cortical thickness in frontal attention areas. Although preliminary, these findings suggest that the impact of AVMs extend beyond the boundaries of the lesion and could cause deficits in global cognitive function, which should be tested more formally and documented to facilitate treatment choice.

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Compliance with ethical standards

Conflict of interest The authors declare they have no conflict of interest.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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