Fronto-parietal and white matter haemodynamics predict cognitive outcome in children with moyamoya independent of stroke

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ABSTRACT

Moyamoya disease is a major arteriopathy characterized by progressive steno-occlusion of the arteries of the circle of Willis. Studies in adults with moyamoya suggest an association between abnormal fronto-parietal and white matter regional haemodynamics and cognitive impairments, even in the absence of focal infarction. However, these associations have not been investigated in children with moyamoya. We examined the relationship between regional haemodynamics and ratings of intellectual ability and executive function, using hypercapnic challenge blood oxygen level-dependent magnetic resonance imaging of cerebrovascular reactivity in a consecutive cohort of children with confirmed moyamoya. Thirty children were included in the final analysis (mean age: 12.55 ± 3.03 years, 17 females, 15 idiopathic moyamoya and 15 syndromic moyamoya). Frontal haemodynamics were abnormal in all regardless of stroke history and comorbidity, but occipital lobe haemodynamics were also abnormal in children with syndromic moyamoya. Executive function deficits were noted in both idiopathic and syndromic moyamoya, whereas intellectual ability was impaired in syndromic moyamoya, even in the absence of stroke. Analysis of the relative effect of regional abnormal haemodynamics on cognitive outcomes demonstrated that executive dysfunction was predominantly explained by right parietal and white matter haemodynamics independent of stroke and comorbidity, while posterior circulation haemodynamics predicted intellectual ability. These results suggest that parietal and posterior haemodynamics play a compensatory role in overcoming frontal vulnerability and cognitive impairment.

Keywords: Cerebrovascular reactivity, moyamoya, stroke, executive function, BOLD MRI CVR

Introduction

Moyamoya disease (MMD) is a major arteriopathy of childhood characterized by progressive steno-occlusion of the arteries of the circle of Willis. When it occurs in association with other conditions such as neurofibromatosis type 1 (NF1) or sickle cell disease (SCD) it is known as moyamoya syndrome (MMS). Clinically, neurological compromise in the form of transient ischaemic attacks (TIA), seizures, ischaemic or haemorrhagic stroke and cognitive decline can occur.

Typically, lenticulostriate collaterals develop at the base of the brain to bypass the occlusion and maintain cerebral blood flow (CBF) and cerebral perfusion pressure (CPP). In addition, CPP is maintained by a drop in vascular resistance mediated by cerebral autoregulatory mechanisms which may be accompanied by systemic hypertension. As the disease progresses, CPP falls, encroaching on cerebrovascular reserve. Tissue oxygen extraction fraction is maximized and further reduction in CPP leads to disruption in tissue metabolism, with the clinical consequence of covert or overt, cortical and/or subcortical arterial ischaemic stroke [1–4]. This state of disrupted haemodynamics, present even in the absence of infarction, is known as 'misery perfusion' and has been demonstrated using nuclear medicine studies such as positron emission tomography and CBF single photon emission computed tomography [5,6]. However, the clinical consequences of this haemodynamic disturbance in paediatric moyamoya have not been clearly demonstrated.

Cognitive decline over time [7–9] are recognized as poor outcomes of paediatric moyamoya [10–13]. However, study findings of cognitive outcomes are often inconsistent. This is partly attributable to the clinical heterogeneity of paediatric moyamoya. For example, demographic and pre-existing clinical factors such as age of onset, laterality, history of stroke or TIA, moyamoya comorbidity, or surgical treatment are likely to influence the cognitive outcomes [7,10,13–17]. Children with NF1 and SCD have recognized complex and wide-ranged cognitive profiles that include normal function, visuo-spatial deficits and executive dysfunction [18–20] in the absence of a diagnosis of moyamoya. This poses a challenge to understanding whether, and if so, to what extent the haemodynamic consequences of the moyamoya vasculopathy impact cognitive outcomes in children with MMS. However, several studies in adults and children with moyamoya (MMD and MMS) suggest an association between moyamoya and cognitive outcomes, including progressive cognitive decline independent

of the presence of radiologic infarction [7,21,22]. These observations suggest the presence of a different pathophysiological mechanism for the cognitive impairments than the focal stroke itself.

Advanced non-invasive functional neuroimaging techniques can be used to assess cerebral haemodynamics in children with moyamoya. Cerebrovascular reactivity (CVR), defined as a change in CBF in response to vasodilatory stimuli such as a hypercapnic challenge, can be measured using blood-oxygen-level-dependant (BOLD) MR imaging in the clinical setting. Hypercapnic challenge BOLD MRI CVR provides an *in vivo* marker of cerebrovascular reserve in patients with cerebrovascular disease [23–25]. A negative response to vasodilatory stimulus and reduction in regional CBF, termed "steal", indicates a maximized compensatory response and potential vulnerability to a haemodynamic challenge, which suggests tissue at risk of ischaemic injury [26,27]. Qualitative and quantitative measures of BOLD MRI CVR have been shown to correlate with impaired CBF and predict the risk of stroke [23,28–31]. In addition, quantitative CVR indices can be used to demonstrate the extent of steal within the primary diseased vascular territory and adjacent territories [32,33].

Advantages of the BOLD MRI CVR technique include its safety profile, particularly when compared to nuclear medicine techniques, and overall simplicity allowing for repeated assessments in children in the clinical setting [23,34]. In particular, the breath-hold CVR technique (BH-CVR), in which endogenous alveolar carbon dioxide naturally accumulates during short periods of voluntary apnoea, can be more readily implemented in children and is well-tolerated [34].

In the present study, we aimed to determine whether there was an association between abnormal haemodynamics, as measured by BH-CVR, intellectual ability and executive function in children with moyamoya, with and without arterial ischaemic stroke. We hypothesised that in children with moyamoya, cognitive impairments and regional CVR abnormalities would be observed even in the absence of stroke, particularly in the frontal and deep white matter regions. Specifically, given the functional neuroanatomical relationship of executive function within the fronto-parietal and white matter regions, we hypothesised that haemodynamic abnormality in these regions would be more associated with executive function than intelligence. We also hypothesised that regional CVR abnormalities and cognitive impairments would be worse in children with MMS compared to children with MMD.

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Materials and Methods

Participants

A consecutive cohort of children with angiographically confirmed moyamoya, who had BH-CVRs and neuropsychological assessments performed as part of standard institutional practice between 2000 and 2019, were included. For the purpose of this study, moyamoya was defined according to 'The Guidelines for Diagnosis and Treatment of Moyamoya Disease (Spontaneous Occlusion of the Circle of Willis) [34]. Children with a comorbidity such as NF1 or SCD were diagnosed as having moyamoya syndrome (MMS). Institutional practice included: one to two-yearly BOLD MRI CVR studies from time of moyamoya diagnosis to time of transition to adult services (age 18 years) and standardized neuropsychological assessments at two to three developmental time points (typically school entry: 4-6 years; middle school: 8-10 years; and/or high school: 14-18 years). Children with CVR performed under general anaesthesia, 0-6 months post revascularization surgery or with a history of whole brain radiation therapy were excluded (Supplementary Figure 1).

Structural and Functional MRI Acquisition

MRI data were acquired using a 1.5 or 3.0-Tesla clinical MRI scanner (Achieva, Philips, Best, the Netherlands) equipped with an 8-channel head coil. A high-resolution 3D T1-weighted structural scan [160 slices; voxel size=0.86×0.86×1mm^3; FOV=220mm], and an axial T1 scan [25 slices; voxel size=0.43x0.43x7 mm^3; FOV = 220 mm] were acquired for tissue classification.

The BH-CVR MRI protocol consisted of two separate BOLD acquisitions using an EPI-GRE sequence lasting 6.1 minutes each [25 slices; TR/TE=2000/30ms; voxel size=3.4×3.4×5mm3; FOV=220mm; 180 dynamics].

Breath-Hold CVR

The BH-CVR study protocol used has been previously described [23]. Briefly, each BH paradigm began with 10 seconds of normal breathing and then comprised of five 60-second blocks, in which breath-holding and normal breathing were alternated. The breath-holding duration was calculated by subtracting from 60 seconds in each

block (Supplementary Figure 2). To assess subject compliance and motion, we monitored real-time respiration signals using respiratory bellows throughout the scan. Patients who deviated from the instructions (i.e. unable to breath-hold and/or breathe normally when instructed by the research technologist or observed to move excessively) were flagged as 'non-compliant'.

Data processing

All MRI data was transferred to an independent workstation for further processing. Post-processing was performed using Analysis of Functional Neuro Images (AFNI, V. 16.1.04; http://afni.nimh.nih.gov/afni) and FSL (V. 4.1.9; (http://www.fmrib.ox.ac.uk/fsl). The first two dynamics of the BOLD data were truncated and the remaining CVR volumes were corrected for slice-timing, head motion and smoothed by a 2D 7 mm full width half maximum Gaussian kernel. Band pass filtering was performed at lower and upper cut off frequencies of 0.01 and 0.2 Hz. Maximum displacement measurements for each volume were estimated during head motion correction from the six rigid body motion parameters and regressed from the data as covariates in a generalized linear model. Volumes with a maximum displacement exceeding 1.5 mm were censored and data from participants for whom more than 1/3 of the volumes were lost were considered poor quality studies. These studies were excluded from further analysis.

CVR Estimation

For CVR maps, the patient's BOLD time-series in each voxel of the brain was subjected to a generalized linear model, using the expected haemodynamic responses in cerebellar time course as a regressor. The stroke lesion was not included in the CVR estimation. The regression coefficients (or the β weights) were then calculated for each voxel [23,31]. Negative β weights describing an inverse relationship with the regressor represented the steal phenomenon (Supplementary Figure 3). CVR maps consisting of voxel wise negative and positive β weights (describing negative or positive relations with the regressor, respectively) were co-registered to the MNI space using each patient's T1 image.

To generate quantitative indices, the fractional voxel counts of negatively reacting voxels ($f$neg) were computed [23,31] and summarized across cortical regions (frontal, parietal, temporal and occipital) and brain tissue type (grey and white matter) in each hemisphere as defined using the Harvard-Oxford Atlas. Using the normative means from institutional healthy control data, more than 10% of voxels with negative reactivity were considered to represent significant steal and was the study definition of abnormality in CVR [23] (Supplementary Table 1).

Radiographic Moyamoya Characteristics

Conventional contrast and three-dimensional time-of-flight magnetic resonance angiography images were reviewed by an experienced neuroradiologist (MSh or PM). Ischaemic infarction was described as acute or remote and by pattern of infarction (i.e. cortical, cortical watershed, deep watershed) [35]. Moyamoya laterality was recorded and moyamoya severity staged using Suzuki criteria, in which stage 1 to 3 are considered as early stage of disease, compared to stage 4 to 6 [36].

Cognitive Assessments

Children aged between 6 and 16 years of age were administered the Wechsler Intelligence Scale for Children Third Edition (WISC-III) [37] or the WISC Fourth Edition (WISC-IV) [38]. Children who were 16-years or older at the time of assessment completed the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) [39]. All the Wechsler scales provide index scores for overall intellectual ability (Full-scale IQ [FSIQ]), Verbal Comprehension (VCI), Perceptual Reasoning (PRI), Working Memory (WMI), and Processing Speed (PSI), with a normative mean score of 100 and a SD of 15.

Executive function was assessed using the Behavior Rating Inventory of Executive Function (BRIEF), a standardized questionnaire completed by parents, which evaluates multiple aspects of executive function [40]. For participants aged 6 to 18 years, the school-age version was used which provides index scores for emotional–behavioral symptoms (Behavior Regulation/Inhibitory Self-Control Index ⁄ [BRIS]) and cognitive symptoms (Metacognitive Index [MI]) of executive dysfunction, as well as an overall index of executive impairment (Global Executive Composite [GEC]). The normative sample has a mean of 50 and a standard deviation (SD) of 10. High

scores indicate greater difficult, with scores of 60 or greater considered significantly elevated and indicative of clinically-relevant impairment [40]. Wechsler intellectual scores and BRIEF executive function scores matched to the closest CVR date within two years were used for analysis [23].

Statistical Analyses

Descriptive statistics (mean and standard deviation) were used to summarize CVR measures and cognitive outcomes. To determine whether sample means were statistically different from the normative means and to explore the differences in CVR estimates (regional $f$neg values) and cognitive outcomes according to clinical presentation, parametric (one sample t-tests, independent t-tests, paired t-test) and non-parametric (Mann-Whitney U test, Kruskal-Wallis H test, Wilcoxon Signed Rank Z test) were used, as appropriate. We used regional $f$neg values, as the reproducible relationship between CVR and regional $f$neg values has been established in the previous studies [23,31]. Before examining relative effects of regional CVR negativity across cortical lobes and white matter on cognitive outcomes, Spearman's rho correlation analyses were conducted to inspect the associations between these two variables. For the relative effects of regional CVR negativity on intellectual ability and executive function, the regional $f$neg values (bilateral frontal, parietal, temporal, occipital and white matter regions) were entered into multivariable stepwise linear regression models to predict cognitive outcomes while controlling for age, sex, comorbidity, the presence of stroke and moyamoya laterality. Only regional $f$neg values were included in the model to avoid multicollinearity issues of CVR estimates, and VIF (variance inflation factor) scores and tolerance values were examined. Scatterplots and P-P plots were used to determine linear associations between independent and dependent variables, as well as homoscedasticity and normal distribution of the residuals. Durbin-Watson statistics and Cook's distance values were also used to determine independence of the residuals and identify outliers. Statistical analyses were performed using SPSS version 26 software. The statistical significance was held at p<0.05, and corrected for multiple testing using the Benjamini-Hochberg false discovery rate in associations between CVR and cognitive outcomes.

Results

Demographics and Clinical Description

In the final analysis, thirty children with BH-CVRs and standardized neuropsychological assessments conducted within two years (median 0.37 years, range 0 to 1.96 years) met inclusion criteria (Supplemental Figure 1). Three children contributed two studies each. These studies were two to six years apart and had matched unique neuropsychological assessments. Demographics, clinical descriptions of the patients, and cognitive profiles are given in Table 1. Detailed medical history and background information in each case were presented in Supplementary Table 2. The mean age at BH-CVR was 12.6 years (SD = 3.0 years, range 6.5 – 17.1 years, median 12.62 years). Of 30 patients, 15 were diagnosed with moyamoya disease [MMD] and 15 with moyamoya syndrome [MMS: 12 NF1, 3 SCD]. Moyamoya laterality was bilateral in 17 (55%), right-sided in 6 (24%) and left-sided in 7 (21%). Seventeen (56.7%) presented with symptomatic stroke (MMD=9, MMS=8), four of whom had preceding TIAs (MMD=3, MMS=1). The MR imaging pattern of stroke (MM/stroke) was cortical watershed in all 17 children: 5 bilateral, 6 left and 6 right hemispheric. Amongst the 17 children, four had additional findings of silent multifocal deep watershed infarction and one infarction in the left frontal cortex. None of the children included in the study had haemorrhagic stroke. Of the 13 children without stroke (MM/no stroke: MMD=6, MMS=7), 5 had TIAs, 4 were asymptomatic, two had headache, and two presented with other neurological symptoms (one with a movement disorder and one with syncope of unknown aetiology). MR imaging of the 13 children without clinical stroke revealed remote infarcts in two.

Comparisons of Regional CVR negativity

Descriptive CVR estimates are summarised by brain region and tissue (specifically white matter) (Supplementary Table 3) and the regional $f$neg values were compared by presence or absence of moyamoya, stroke, moyamoya laterality, and comorbidity.

Regional CVR negativity, stroke and no stroke

All regional *f*neg values in summaries of brain region and tissue were higher in children with MM/stroke and MM/no stroke when compared to the normative means, and children with MM/stroke had higher *f*neg values compared to children MM/no stroke (Table 2). However, these differences did not reach significance. (Supplementary Figure 4). Frontal lobe *f*neg was greater when compared to *f*neg in the parietal (Z=-3.47, p=0.001), temporal (Z=-2.382.65, p=0.021), and occipital lobes (Z==-4.31, p<0.001), demonstrating frontal predominance of CVR abnormality, and an anterior-posterior gradient across all patients (Figure 1A). These differences were more pronounced in children with MM/stroke, specifically in the prefrontal region along with the frontal midline (coloured in bright yellow in Figure 1B top), but also observed in children with MM/no stroke (Figure 1B bottom). Supplementary Figure 5 shows images of T2-FLAIR, breath-hold CVR, Angiography in two cases of children with and without stroke.

Regional CVR negativity and Moyamoya laterality

Comparison of *f*neg values by hemisphere in all (MM/stroke and MM/no stroke) unilateral moyamoya cases (N=13, 43%) demonstrated significantly higher *f*neg in the moyamoya hemisphere compared to the non-moyamoya hemispheric brain regions: frontal (Z=-2.62, p=0.018), parietal (Z=-2.69, p=0.021), and temporal (Z=-2.27, p=0.023).

Regional CVR negativity and comorbidity in no stroke group

The effect of comorbidity was examined in thirteen children with MM/no stroke (MMD=6, MMS-NF1=7). Children with MMD and MMS-NF1 demonstrated elevated CVR negativity predominantly in the frontal region. In addition, *f*neg values were significantly higher in children with NF1 compared to children with MMD, in the right occipital lobe (U=35, p=0.046) (Supplementary Figure 6).

Cognitive Outcomes

Descriptive statistics for cognitive outcomes are presented in Table 3. The standardized scores of cognitive outcomes ranged from average to severe impairment across the patients. Using the one sample t-test, children with moyamoya demonstrated significantly lower performance in all five IQ indices and greater impairments in two of the three executive function summary scores (Metacognitive Index and Global Executive Composite) compared to the normative mean.

Cognitive outcomes, stroke and no stroke

Between group comparisons of stroke vs. no stroke means in IQ and executive function indices demonstrated lower cognitive performance overall in children with MM/stroke. These differences were statistically significant for Verbal Comprehension Index (VCI) in children with unilateral and bilateral stroke (H(3)=8.27, p=0.04) (Supplementary Figure 7A). ~~In addition, children with moderate severity (Suzuki stage 3 and 4) in the left hemisphere revealed mean VCI scores, about 10 points lower (Mean=91.44, SD=8.68) than children with mild severity (Suzuki stage 0 to 2) in the left hemisphere (Mean=81.75, SD=17.04) (Supplementary Figure 7B).~~

Cognitive outcomes and moyamoya laterality

These were no significant differences in cognitive outcome between children with bilateral and unilateral moyamoya.~~except in metacognitive index scores which were marginally higher in children with bilateral moyamoya (U=24.5, p=0.056).~~

Cognitive outcomes and comorbidity in no stroke group

The effect of comorbidity on cognitive outcome was examined by comparison of the children with MMD and MMS in the no stroke group. Since all children with MMS-SCD in our study had ischaemic stroke, they were excluded from this analysis. Executive function scores were abnormal (one SD above the normative means) in children with MMD, while IQ scores were in the normal range. Children with MMS-NF1 deviated approximately

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one SD from the normative means in the majority of IQ and EF scores (Supplementary Figure 8). Between group comparisons revealed significant differences in the following IQ indices: FSIQ, U=2.0, p=0.005; VCI, U=3.0, p=0.008; PRI, U=1.5, p=0.009. Executive function scores were not different in the MMD group (mean BRIEF-GEC=61.40, SD=15.37) compared with the NF-1 group (Mean BRIEF-GEC=59.67, SD=14.84; p=0.93) (Supplementary Table 4).

Regional CVR negativity and cognitive outcome

The correlations between regional CVR negativity and cognitive outcomes in the whole group are presented in Supplementary Table 6. Different IQ measures were correlated with CVR negativity of multiple cortical and white matter regions, which remained significant with correction for multiple comparisons, while none of the correlations with EF measures survived correction for multiple comparisons. In the independent analysis of children with and without stroke, right parietal CVR negativity was significantly associated with the VCI in IQ (ρ=-0.842, p=0.001) in children without stroke, and with GEC in EF (ρ=0.822, p=0.04) in children with stroke.

The relative effects of regional negative CVR by cortical lobes and white matter on intellectual ability and executive function were explored in multivariable stepwise regression analyses without (non-adjusted) and with (adjusted) controlling for covariates (age, sex, comorbidity, stroke presentation, and moyamoya laterality). In the non-adjusted model, the role of right white matter CVR negativity was remarkable in explaining both IQ and EF across the patients, while this effect remained significant only in EF in the adjusted model.

Without controlling for covariates, three measures (FSIQ, VCI, WMI) in IQ and two measures (MI, GEC) in EF were explained by the CVR negativity in the right white matter (FSIQ, B=-85.11, p=0.01; VCI, B=-73.11, p=0.005; WMI, B=-55.75, p=0.047; MI, B=55.06, p=0.042; GEC, B=57.79, p=0.046), suggesting this region may be affected by the moyamoya condition in general and linked to these cognitive outcomes. The PRI in IQ was associated with CVR negativity in the right occipital lobe (B=-97.88, p=0.022) while the PSI in IQ with CVR negativity in the left white matter (B=-59.23, p=0.027). The BRIS in EF was associated with the CVR negativity in the right parietal lobe (B=70.81, p=0.005) (Supplementary Table 6).

Upon controlling for covariates, the effects of right parietal CVR negativity on BRIS (B=70.81, p=0.005) and white matter CVR negativity on MI and GEC (B=55.06, p=0.056; B=57.79, p=0.028) remained the same across three EF measures (Figure 3A). In contrast, the effects of the right white matter CVR negativity were no longer significantly associated with IQ measures. FSIQ and VCI were associated with the right occipital lobe CVR negativity (FSIQ, B=-64.07, p=0.038; VCI, B=-60.58, p=0.027) (figure 3B), WMI with left white matter CVR negativity (B=-56.51, p=0.005), and PSI with the left frontal lobe CVR negativity (B=-39.79, p=0.029). PRI was not associated with regional CVR negativity but only explained by comorbidity (Table 4).

Exploratory analysis was conducted of each moyamoya group (MMD and MMS-NF1) separately, to determine the relative effect of comorbidity on the observed association between CVR estimates and cognitive outcomes. MMS-SCD patients (n=3) were excluded in this exploratory analysis as they represented the most severe cases in our cohort with ischaemic stroke with greatest CVR negativity and lowest performance overall in cognitive outcomes. The main differences were found in the relative effects of cortical regional negative CVR on the IQ indices. In the separated analysis of MMS-NF1, the association between occipital lobe CVR negativity and IQ indices was pronounced. This association was not observed in the separated analysis of MMD. Instead, the hypothesised effects of parietal lobe CVR negativity was prominent in explaining both IQ and executive function scores in MMD (Supplementary Table 7).

Discussion

In the present study, we sought to determine whether there was an association between regional cerebral haemodynamics, as assessed by breath-hold BOLD MRI CVR and cognitive impairment, in children with moyamoya. In keeping with our hypotheses, we demonstrated an association between fronto-parietal cortex and white matter CVR abnormality and cognitive impairments, regardless of stroke presentation. Executive function was particularly affected independent of moyamoya subtype and stroke presence. Intellectual ability was largely spared in children with MMD and no stroke, but lower than expected in children with MMS-NF1 and no stroke. Executive dysfunction was associated with all (MMD and MMS) children demonstrating significant frontal haemodynamic abnormality. Poorer cognitive outcomes were associated with posterior circulation moyamoya and abnormal parietal and posterior measures of abnormal CVR in children with MMD. Abnormal posterior

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haemodynamics, specifically of the occipital lobe, were also associated with poorer measures of cognitive outcome in children with MMS-NF1. However, this was independent of posterior moyamoya involvement. Thus, our study highlights the shared frontal vulnerability of the moyamoya condition, the important role of the posterior circulation in maintaining intellectual ability, and the additional impact of NF1 syndrome related posterior circulation vulnerability in children with moyamoya.

Cognitive outcomes, stroke and comorbidity

In our cohort, around 40% of all children showed significant executive function impairments on the metacognitive index and global composite scores, suggesting that executive functioning in daily life is vulnerable in children with moyamoya. Impairments in intellectual ability were also present in 27- 40% of the children, depending on the specific cognitive domain examined. Children with stroke demonstrated greater CVR abnormality than those without stroke, across all regional summaries, and more severe cognitive impairments in both IQ and executive function scores. Of note, abnormal CVR and cognitive impairments were still observed in children with moyamoya and no history of stroke. Furthermore, there was a difference in CVR abnormality and cognitive impairment in the no stroke group by moyamoya subtype. Children with MMD and no stroke exhibited abnormality in CVR and frontal haemodynamics in association with abnormally elevated scores in executive function. However, intellectual ability was within the normal range. These findings are in keeping with previous literature that reports impairment in executive function in adults and children with moyamoya and no history of stroke [7,21]. These findings also provide evidence that regional haemodynamic abnormalities are a plausible mechanism of executive dysfunction in moyamoya. Intellectual ability, mediated by multiple broad cortical-subcortical functional networks, was overall maintained in the no stroke MMD group. However, there was a significant difference in the verbal comprehension ability between children with and without stroke. This may be explained by the asymmetric and predominant involvement of the left internal carotid artery in bilateral moyamoya disease, given its supply of the inferior frontal and superior temporal regions, which are functionally related to verbal ability [41,42]. However, reports of verbal ability in paediatric moyamoya are variable and likely reflect the small sample sizes, heterogeneity of comorbidities and natural history of moyamoya.

Right fronto-parietal and white matter haemodynamic function and executive function

Studies in adults with moyamoya also suggest a relationship between cognitive impairments and regional hypoperfusion in the absence of stroke. Kang *et al*. [43] employed single-photon emission computerized tomography (SPECT) imaging with acetazolamide challenge in a cohort of 27 adults with moyamoya without focal stroke, demonstrating an association between fronto-parietal hypoperfusion and lower visual and auditory performance testing. Similarly, Calviere *et al*. [44] described an association between lower frontal CVR assessed using dynamic susceptibility contrast perfusion magnetic resonance imaging, and cognitive impairment, in a small cohort of adults with MMD (N=10). Su *et al*. [45] reported an association between cerebral perfusion (using SPECT), regional grey and white matter microstructural abnormalities, and cognitive impairment, also in the absence of focal infarction. The critical role of fronto-parietal cortical and white matter regions has also been highlighted by studies examining the functional neural correlates of intellectual ability and executive function in both clinical (e.g., preterm children) [46–49] and non-clinical (typically developing) conditions [50–53].

In our study haemodynamics, as demonstrated by CVR negativity, were most abnormal in the hemisphere directly affected by the moyamoya, the fronto-parietal cortex and white matter, and revealed an anterior-posterior gradient regardless of clinical presentation and moyamoya subtype. Regional comparisons of cerebral haemodynamics between children with MMD and no stroke and children with MMS-NF1 and no stroke demonstrated comparable location of CVR abnormality in the anterior circulation. These predominantly anterior, abnormal regional haemodynamics mirror the functional locations of the cognitive impairments seen in paediatric moyamoya in the absence of stroke, namely executive dysfunction. Moyamoya typically affects the anterior circulation of the circle of Willis and the frontal, parietal and white matter brain regions. The leptomeningeal anastomotic network plays an important role in the collateral supply of the vulnerable anterior circulation [54]. Neuroimaging studies have reported that deficits in executive function are related to damage to the dorsolateral prefrontal cortex and anterior cingulate cortex [55]. Hence, the association between the finding of impaired anterior circulation and executive dysfunction is as expected. Executive function in our study was also consistently associated with right hemisphere CVR indices. Specifically, the right parietal and white matter CVR indices were critical to explain inter-patient variability in executive function while controlling for heterogeneous clinical presentation. This is in-line with previous behavioural and neuroimaging studies that have shown the right hemisphere to be important for attention

and inhibitory control [56,57]. The right inferior frontal gyrus, as a part of the fronto-parietal network, is widely implicated in inhibitory control, as well as in the more general role of attention control, both of which are closely linked to executive function [56], whereas intellectual ability is more globally supported by prefrontal function and other widely distributed brain regions at a network level [58,59]. There is evidence these two psychological constructs, intellectual ability and executive function, relate to and support each other, but are not strongly correlated in standardised test scores, while frontal lesions do not necessarily impair IQ [60,61]. In line with this, our findings of right-sided, frontally predominant, anterior-posterior disrupted haemodynamics associated with abnormal sub-scores of executive function suggest that executive function is impacted by the specific known perfusion vulnerabilities associated with moyamoya. Hence, we suggest that misery perfusion, resulting in fronto-parietal and white matter vulnerability, is likely a contributory mechanism to executive dysfunction in paediatric moyamoya, regardless of the heterogeneous clinical presentation.

Of note, the left-sided frontal and white matter vulnerability was associated with two sub-scores in intellectual ability: working memory index and processing speed index. Working memory is one of the theoretical constructs of executive function and is comprised of flexible thinking and cognitive control. Processing speed is not considered an executive function but is closely linked to executive function as the longer it takes to process information, the longer it takes to perform tasks relating to executive skills. Thus, this is in line with our findings of the association between fronto-parietal and white matter vulnerability and executive function deficit in moyamoya. Neuroimaging studies in congenital heart disease and adult moyamoya disease also support a relationship between frontal and white matter involvement, WMI and PSI [62,63]. The finding of an association between lateralized abnormal haemodynamics and cognitive functions ie., abnormal left haemodynamics, WMI and PSI, compared to abnormal right haemodynamics and parental ratings of executive dysfunction in daily life, may be related to task-specific effects. A possible explanation for this is that WMI and PSI, in the Wechsler intelligence scale, measure ability to attend and manipulate numeric and symbolic information presented verbally and visually. These task-based, behavioural measurements are commonly observed to be left-sided in clinical neuroimaging studies. This is distinct from the BRIEF scale, which is context-based, third-person reported measurements with ecological validity [64–66].

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Spared function of posterior circulation and its compensatory role for cognitive outcomes

The role of the posterior circulation is important to consider in moyamoya. The posterior circulation is often spared, particularly in the early stages of the disease when regional CBF shows a loss of the normal pattern of frontal dominance. In its place, there is normal to increased CBF in the occipital region [67]. The posterior circulation remains able to respond to haemodynamic challenges and compensate for frontal disturbances as long as it is spared [68]. Hence, involvement of the posterior circulation can reflect vascular disease progression [69]. Relative sparing of the posterior circulation, abnormality in anterior circulation haemodynamics and elevated executive function scores was predominantly observed in the MMD and no stroke groups. This likely reflects that these children were in earlier stages of the disease with relative sparing of the posterior circulation vessels. Although children with MMS-NF1 were also in earlier stages of the disease, regional CVR abnormality in this group included that of the posterior circulation, specifically the occipital lobe, in the absence of stroke. Notably, the haemodynamic impairments of MMS-NF1 were associated with both executive function and intellectual ability. Children with MMS-SCD (n=3) had the most advanced vascular disease, stroke and the most significant cognitive impairments in the whole group. Notably, both MMS groups (MMS-SCD and MMS-NF1/no stroke) had occipital lobe CVR abnormality, and low/abnormal IQ scores. Therefore, we argue that disrupted haemodynamics in the anterior circulation and executive dysfunction likely represent the shared moyamoya condition in both (MMD and MMS) groups, whereas the impact of disease severity and comorbidity on the posterior circulation of the brain resulted in additional impairments in intellectual ability.

Occipital haemodynamics and intellectual ability in MMS-NF1

The importance of right occipital lobe involvement in our study was an interesting finding. Functional and structural neuroimaging studies have revealed a prominent role for the right hemisphere, including the occipital lobe, inferior parietal lobe, and dorsolateral prefrontal cortex, in visuo-spatial processing [70]. The inefficient recruitment of the right hemisphere network, in particular the posterior regions, has been suggested as a possible link to recognized functional corollary of visuo-spatial deficits in individuals with NF1 [71,72]. Studies have demonstrated significantly lower cerebral blood flow in patients with NF1, occurring most prominently in the posterior circulation and the border zones of the middle and posterior cerebral arteries, even in the absence of

prior strokes or underlying moyamoya disease [73]. Vasculopathy and associated steno-occlusive changes in the cerebral microvasculature and alteration in cerebral metabolic demand in NF1 patients were suggested by the authors. However, the reasons for more dominant perfusion deficits in the posterior circulation are still unclear. Finally, we note that the cognitive impairments of children with MMS-NF1 observed in our cohort are comparable to reports of children with NF1 and no moyamoya, in which IQ is approximately 1SD lower than the general population [74] and absolute rates of intellectual disability are only modestly elevated [75] (Supplementary Table 5).

Measuring Cerebrovascular Reactivity in Clinical Practice

Cerebral haemodynamics can be measured using transcranial Doppler ultrasound, SPECT and PET [43,44]. However, these techniques are limited by poor spatial resolution, poor reproducibility [45], capital costs and restrictions related to use of nuclear medicine. The voluntary hypercapnic challenge BOLD MRI CVR technique provides an *in vivo* measure of cerebral haemodynamics in children with moyamoya condition. In particular, the breath-hold (BH) technique is safe, simple, and readily implementable in children with moyamoya. The computer-controlled stimulus system can be an alternative hypercapnic challenge for the quantitative assessment of BOLD MRI CVR. The quantification of alveolar gas concentrations by sampling the end-tidal partial pressures of CO_2 from the subject's exhaled breaths provides an accurate measure of CVR in young children, although computer-controlled stimulus delivery relies on specialized equipment which can be a barrier in some clinical settings to the adoption of this technique, [42]. Replication of our current findings is a necessary next step toward providing evidence for the implementation of a potentially important and feasible tool for the assessment of cognitive function, as a measure of pre-stroke ischaemic injury, and an opportunity for primary prevention of the neurological deterioration that is a recognized consequence of this progressive disease.

Study Limitations

The main limitation of our study is the relatively small sample size. In our no stroke cohort, children with MMS-NF1 demonstrated significantly lowered performance in both IQ and executive function, but there were no

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differences between our NF1/no stroke/moyamoya findings and published study data of children with NF1 only. However, to our knowledge, our study is the largest single centre North American cohort of children with this relatively rare condition, in whom functional BOLD MRI CVR imaging and neuropsychological assessments were conducted as standard of care in a consecutive cohort of children regardless of presentation. Multi-centre collaboration is needed to achieve larger numbers and to investigate longitudinal effects of disease on cognitive outcomes.

The neuropsychological assessment that we used in this study included standardized and validated performance-based testing and parental report for daily-based behaviours. These provided standardized norms to understand the impact of the disease condition(s) on an individual's cognitive profile. However, intellectual ability and executive function only explain very basic cognitive function and have limitations to capture complex cognitive decline process in each individual. Thus the findings in this study should be interpreted and applied in a limited manner in describing the associations between cerebral haemodynamics and cognitive outcomes.

Conclusions

In summary, our findings suggest that executive dysfunction is associated with fronto-parietal and white matter haemodynamics, while posterior circulation haemodynamics are associated with intellectual ability. Finally, our study suggests that parietal and posterior haemodynamics play a role in the prevention of cognitive impairment and ischaemic brain injury.

Acknowledgements

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Figure legends

Figure 1. *f*neg summarized by cortical lobes in children with and without ischaemic stroke

(1A) Frontal, parietal, temporal and occipital *f*neg values averaged bilateral information were summarized in children with and without ischaemic stroke. In both groups, significantly high CVR negativity (*f*neg > 10%) was observed across all cortical regions. There were no significant differences between the groups, but frontal *f*neg values were significantly greater compared to other cortical regions; (1B) The CVR negativity was more pronounced in children with stroke, specifically in the prefrontal region, which extended along the frontal midline (coloured in bright yellow), but these differences did not differ significantly in children with and without stroke.

Figure 2. The association between the regional *f*neg and cognitive outcomes

(2A) *f*neg in the right occipital region was significantly associated with full-scale IQ score regardless of the stroke history and comorbidity; (2B) *f*neg in the right white matter region was significantly associated with global executive function score regardless of the stroke history and comorbidity.