Measuring Quantitative Cerebral Blood Flow in Healthy Children: A Systematic Review of Neuroimaging Techniques

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Cerebral blood flow (CBF) is an important hemodynamic parameter to evaluate brain health. It can be obtained quantitatively using medical imaging modalities such as magnetic resonance imaging and positron emission tomography (PET). Although CBF in adults has been widely studied and linked with cerebrovascular and neurodegenerative diseases, CBF data in healthy children are sparse due to the challenges in pediatric neuroimaging. An understanding of the factors affecting pediatric CBF and its normal range is crucial to determine the optimal CBF measuring techniques in pediatric neuroradiology. This review focuses on pediatric CBF studies using neuroimaging techniques in 32 articles including 2668 normal subjects ranging from birth to 18 years old. A systematic literature search was conducted in PubMed, Embase, and Scopus and reported following the preferred reporting items for systematic reviews and meta-analyses (PRISMA). We identified factors (such as age, gender, mood, sedation, and fitness) that have significant effects on pediatric CBF quantification. We also investigated factors influencing the CBF measurements in infants. Based on this review, we recommend best practices to improve CBF measurements in pediatric neuroimaging.

Level of Evidence: 1

Technical Efficacy: Stage 2

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Cerebral blood flow (CBF) is essential for the delivery of oxygen, glucose, and nutrients to brain tissues.[1] It is also an important hemodynamic parameter to identify many cerebrovascular and neurological disorders, such as stroke and dementia.[2–4] Several medical imaging techniques have been developed to quantify CBF in absolute units (such as mL/100 g/min) including the gold standard modality ^{15}O-water positron emission tomography (PET), arterial spin labeling (ASL) magnetic resonance imaging (MRI), dynamic susceptibility contrast (DSC) MRI, phase contrast (PC) MRI, and ^{133}Xenon SPECT. For example, Fig. 1 shows the CBF maps acquired by these modalities from a healthy female subject (19 years old) using a simultaneous PET/MRI system. In PET and SPECT, a radiotracer is administered to the patient, and its dynamic is monitored using a time activity curve.[5,6] In DSC MRI, a bolus of gadolinium-based contrast agent is administered intravenously to allow the tracer to pass through the capillary bed in the brain. MR images are acquired using T2*-weighted sequences to derive such hemodynamic parameters as relative CBF, cerebral blood volume (CBV), and transit time.[7] In ASL, an endogenous tracer is created by magnetically labeling the blood water and MR images in the brain are acquired to capture the dynamics of the labeled blood water.[8] Voxel-wise CBF can be quantified by fitting the acquired imaging data to kinetic models.[9] In PC MRI, whole brain CBF can be measured by the total flow volume in the internal carotid arteries (ICAs) and vertebral arteries (VAs) scaled by the volume of the brain tissue.[10] While these techniques have been widely applied to measure

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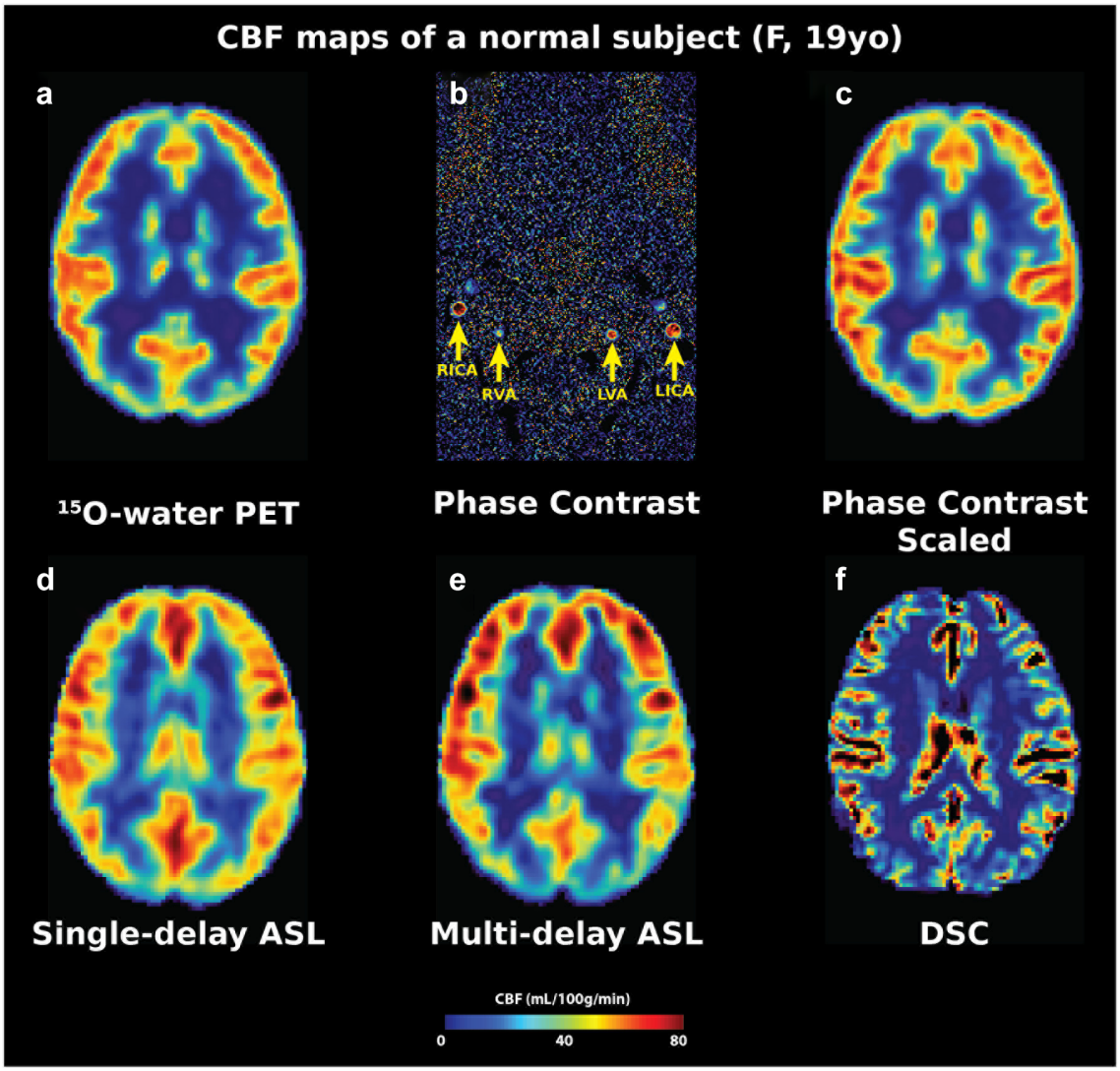

FIGURE 1: CBF maps of a normal subject (female, 19 years old). (a) CBF measured by ^{15}O-water PET; (b) phase contrast map showing right internal carotid artery (RICA), right vertebral artery (RVA), left vertebral artery (LVA), and left internal carotid artery (LICA). The flow volume in these vessels is used to compute CBF; (c) CBF map measured using the flow volume values; (d) CBF map measured by single-delay ASL; (e) CBF map measured by multi-delay ASL (five PLDs); (f) CBF measured by DSC MRI.

CBF in adults,[11,12] there is a paucity of data on the assessment of CBF in the pediatric population. Specifically, the normal range of CBF in different ages and its relationship with normal brain development remains to be elucidated. Although several confounding factors, such as age, gender, and mood, have been identified to affect CBF measurements in adults,[13] their impact on pediatric CBF measurements is unknown. CBF measurement techniques and potential biases in imaging modalities may also affect the accuracy of CBF measurements. Additionally, the intrinsic characteristics of the pediatric population, such as physical size, age, and brain development, may also affect the choice of imaging technique to assess pediatric CBF. An understanding of how such factors affect pediatric CBF measurements and its normal range is crucial to determine the optimal CBF measuring techniques in pediatric neuroradiology.

Since several imaging techniques have been used to measure pediatric CBF, it is not surprising that a wide range of CBF values has been reported in healthy children. We define the factors (such as the type of imaging modality and scanning parameters) associated with the experimental design and facilities as technological factors. In addition, CBF results may also depend on other factors, such as the age and gender of the participants and whether the subject is being sedated during the scan. We define these intrinsic characteristics of the subjects as physiological factors. It is important to understand the impact of these factors to enhance the experimental design and improve the accuracy of pediatric CBF measurements in clinical applications. This work is a systematic review focused on factors affecting pediatric CBF in normal subjects, using the preferred reporting items for systematic reviews and meta-analyses (PRISMA) framework.

Methods

The systematic review process followed the PRISMA guideline developed by Moher et al.[14] Our literature search included subject headings and keywords for two key concepts: 1) CBF and brain perfusion; 2) pediatrics, children, adolescence, and teenagers. The search was developed in PubMed and then adapted for the additional information sources for other databases. The complete keywords of the search strategy for each literature database can be found in Supplementary Materials. The relevant search query was performed in PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/#search), and Scopus (https://www.scopus.com/search/) on December 15, 2021. No date limits were placed on the search. Animal studies, conference papers and abstracts, editorials, narrative reviews, and studies that were not written in English were excluded from the search results.

Four steps were performed to select the relevant studies from the search results. Step 1: all duplicated search results were identified and merged. Step 2: the title and abstract of each study were screened using the Covidence software (Covidence, Melbourne, Australia) with the inclusion and exclusion criteria shown in Table 1 independently applied by two authors (MYZ and RDA) of this work. The criteria were reviewed and confirmed by a board-certified pediatric neuroradiologist (ET) of this paper. Studies that did not satisfy these criteria were excluded. If the two screening authors cannot decide the relevance of a particular study based on the title and abstract information only, such a study would be retained for further screening in the next step. Step 3: the full text of the selected studies in Step 2 was screened using the same inclusion and exclusion criteria. All conflicts of opinion were resolved to decide the relevance of each study. The number of papers excluded was recorded for each exclusion criterion as shown in Table 1. Step 4: the studies selected from Step 3 formed the collection of studies for data extraction. Information extracted from the selected studies included the year of publication, name of the journal, the aim of the study, demographic information of the study subjects, sample size, experimental conditions, imaging modality, data analysis method, CBF measurement, and conclusions.

TABLE 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Peer-reviewed journal articles	Conference abstracts, conference papers, editorials, review papers, and case reports
Human studies including normal subjects	Animal and phantom studies, human studies including patients
Age of subjects younger than 18 years	Age of subjects older than 18 years
Subjects including full-term infants	Subjects excluding full-term infants
Sample size larger than 2	Sample size less than 2
Quantitative CBF values reported	Quantitative CBF values not reported
English language	Non-English language
Full text available	Full text unavailable

Results

Summary of Literature Search

As shown in Fig. 2, after conducting the literature search using the inclusion and exclusion criteria, we found 3875 papers, 1759 of which were duplicates and removed, resulting in 2116 studies for the initial title and abstract screening. Subsequently, we excluded an additional 2020 studies because they were irrelevant to the aim of this systematic review. The remaining 96 papers were screened by reading their full text, and 64 were excluded for reasons such as no CBF values reported, unknown sample size, and no access to the original paper in the study. From this, there were 32 articles retained, and these formed the basis for the rest of this systematic review, as shown in Table 2.

These selected 32 articles investigated the CBF in a total of 2668 subjects (age at the time of scan ranging from 1 day to 18 years old). All studies applied MRI (at 1.5 T, 3 T, and/or both) to measure CBF in absolute units (mL/100 g/min) using ASL and/or PC MRI. Among the 31 studies that employed ASL MRI, 25 of them used a single post-label delay while 6 studies used multiple post-label delays. There were seven studies that used PC MRI and one study that used ^{15}O-water PET. Among the 28 studies that indicated the number of males and females, there were 1233 males and 1271 females. There were 11 studies that investigated CBF in subjects younger than 1 year.

CBF Measurements in Children Older Than 1 Year

Figure 3 shows the whole brain CBF measurements in children older than 1 year from seven studies. The remaining 25 studies reported regional CBF only. Overall, the whole brain CBF values in these seven studies were between 22 and 141 mL/100 g/min. The lowest CBF measurement reported was 22 mL/100 g/min in a study that compared the effects of sedation using propofol and a combination of propofol and ketamine on pediatric CBF[45] while the highest CBF

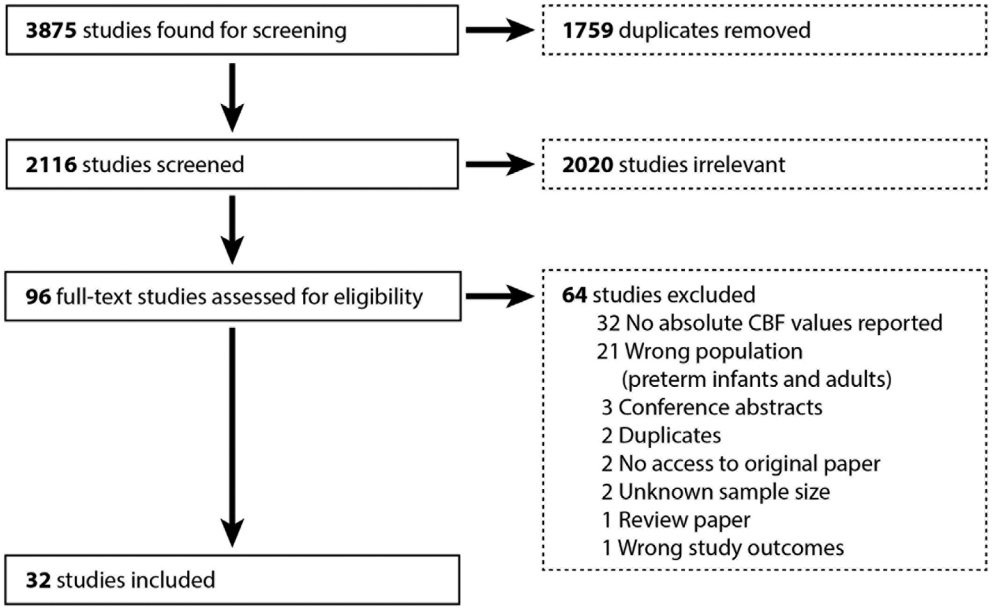

FIGURE 2: Literature search and screening results from three databases PubMed, Embase, and Scopus. After removing the duplicated papers, the title, abstract, and full text of each study were assessed using the inclusion and exclusion criteria.

measurement (141 mL/100 g/min) was found in a study that investigated the hemodynamics during developmental trajectory in children aged between 7 and 18 years using PC MRI.[4] Two studies reported the whole brain CBF for subjects aged between 7 and 17 years, with ranges between 40 and 87 mL/100 g/min[41] and 30 and 103 mL/100 g/min.[24]

Figure 4 shows the gray matter (GM) CBF measurements in children aged older than 1 year. The distribution of GM CBF in these studies was between 20 and 109 mL/100 g/min. In a study that investigated the effect of puberty on perfusion during adolescence from 10 to 18 years, the GM CBF in 922 subjects of the Philadelphia Neurodevelopmental Cohort was reported to be between 33 and 109 mL/100 g/min using ASL.[28] In another study that investigated 23 subjects in a similar age range (9–18 years, $N = 23$), the GM CBF was between 20 and 60 mL/100 g/min measured by multi-delay ASL.[30]

Figure 5 shows the white matter (WM) CBF distribution in children aged 1 year or older. The range of WM CBF values in five selected studies was between 15 and 50 mL/100/min. Among these results, Leung et al showed that WM CBF measured by multi-delay ASL demonstrated the largest range: 15–50 mL/100/min in 23 subjects aged between 9 and 18 years.[30] In another study that reported the pediatric WM CBF in a broader age group but a similar sample size ($N = 23$), WM CBF was between 21 and 27 mL/100 g/min measured by single-delay ASL.[16] Due to the intrinsic low SNR of ASL signal in WM, care should be taken when interpreting WM CBF data obtained by ASL.

Among the various factors affecting CBF, age was the most frequently investigated and appeared in 11 studies.[4,15,16,18–20,27,30,40,41,43] In general, these studies found that CBF increased with age from birth to around 7–10 years and then it declined steadily until 18 years old. However, another study reported that CBF measured by ASL was not significantly related to age among subjects between 1 month and 10 years.[15] In terms of the ASL CBF difference between males and females, Taki et al showed that GM CBF in females aged between 5 and 18 years was significantly higher than in males after partial volume correction.[23] In a study that investigated the effect of puberty on CBF using the Philadelphia Neurodevelopmental Cohort, it was found that after reaching its peak at around 10 years old, CBF in males declined until adolescence while in females it declined until mid-adolescence but increased thereafter.[28] Regional CBF decreases in the medial frontal gyrus and insula were linked with the consumption of cannabis among teenagers aged 16–18 years.[26] Hunger or starvation for at least 6 hours was found to decrease CBF in the bilateral posterior insula among both male and female adolescents aged between 13 and 15 years; CBF in these regions increased significantly after food consumption.[42]

In terms of CBF measurements across multiple modalities, Jog et al found that whole brain CBF was between 37 and 141 mL/100 g/min and between 46 and 98 mL/100 g/min measured by PC and single-delay ASL respectively among 91 subjects in the Philadelphia Neurodevelopmental Cohort.[4] Although Makki et al reported whole brain CBF between 23 and 82 mL/100 g/min measured using MRI at 1.5 T and 3 T, there was no direct comparison of CBF measured at different field strengths on the same cohort.[45]

TABLE 2. Pediatric CBF Studied Included in This Review

Study	Authors	Study Cohort	Imaging Modality	ASL Technique
1.5 T				
	Wang et al[15]	$N = 7$; age: 1 month to 10 years; 6 males	ASL	Multi delay
	Biagi et al[16]	$N = 23$; age: 4–18 years; 10 males	ASL	Single delay
	Wang et al[17]	$N = 19$; age: 7–13 months; no sex information	ASL	Single delay
	Hales et al[18]	$N = 16$; age: 8–18 years; 7 males	ASL	Multi delay
	Carsin-Vu et al[19]	$N = 84$; age: 6 months to 15 years; 40 males	ASL	Multi delay
	[a]Zun et al[20]	$N = 22$; age: 40–44 weeks; 13 males	ASL	Single delay
3 T				
	[a]Miranda et al[21]	$N = 6$; age: 2 days; no sex information	ASL	Single delay
	Taki et al[22]	$N = 202$; age: 5.7–18.4 years; 95 males	ASL	Multi delay
	Taki et al[23]	$N = 202$; age: 5.7–18.4 years; 95 males	ASL	Multi delay
	Kilroy et al[24]	$N = 39$; age: 7–17 years; 14 males	ASL	Single delay
	Jain et al[25]	$N = 22$; age: 7–17 years; 15 males	ASL and PC	Single delay
	Jacobus et al[26]	$N = 46$; age: 16–18 years; 36 males	ASL	Single delay
	[a]Duncan et al[27]	$N = 61$; age: 110–136 days; 37 males	ASL	Single delay
	Satterthwaite et al[28]	$N = 922$; age: 10–18 years; 404 males	ASL	Single delay
	Kandel et al[29]	$N = 88$; age: 7–18 years; no sex information	ASL	Single delay
	Jog et al[4]	$N = 91$; age: 7–18 years; 44 males	ASL and PC	Single delay
	Leung et al[30]	$N = 23$; age: 9–18 years; 7 males	ASL	Multi delay
	Chaddock-Heyman et al[31]	$N = 73$; age: 7–9 years; 32 males	ASL	Single delay
	Forkert et al[32]	$N = 100$; age: 4 months to 18 years; 39 males	ASL	Single delay
	[a]Tortora et al[33]	$N = 11$; age: 40–41 weeks; 5 males	ASL	Single delay
	[a]Bouyssi-Kobar et al[34]	$N = 104$; age: 40–42 weeks; 58 males	ASL	Single delay
	[a]Ouyang et al[35]	$N = 30$; age: 40–43 weeks; 10 males	ASL and PC	Single delay
	Pontifex et al[36]	$N = 41$; age: 9–11 years; 23 males	ASL	Single delay
	[a]Liu et al[37]	$N = 25$; age: 34–114 weeks; 22 males	PC	
	[a,b]Andersen et al[38]	$N = 4$; age: 1–3 days; 4 males	ASL and ^{15}O-water PET	Single delay
	[a]Wang et al[39]	$N = 60$; age: 1–15 days; 34 males	ASL	Single delay
	[a]Wong et al[40]	$N = 49$; age: 0-3 years; no sex information	ASL	Single delay
	Paniukov et al[41]	$N = 96$; age: 1.97–6.9 years; 50 males	ASL	Single delay

TABLE 2. Continued

Study	Authors	Study Cohort	Imaging Modality	ASL Technique
	Charroud et al[42]	$N = 15$; age: 13–15 years; 8 males	ASL	Single delay
	Zou et al[43]	$N = 97$; age: 13–14 years; 58 males	ASL and PC	Single delay
	[a]Qi et al[44]	$N = 9$; age 38–42 weeks: 7 males	ASL and PC	Single delay
1.5 T and 3 T				
	Makki et al[45]	$N = 81$; age: 3 months to 10 years; 35 males	ASL and PC	Single delay

[a]Indicates studies including infants.
[b]Indicates studies using both MRI and PET.

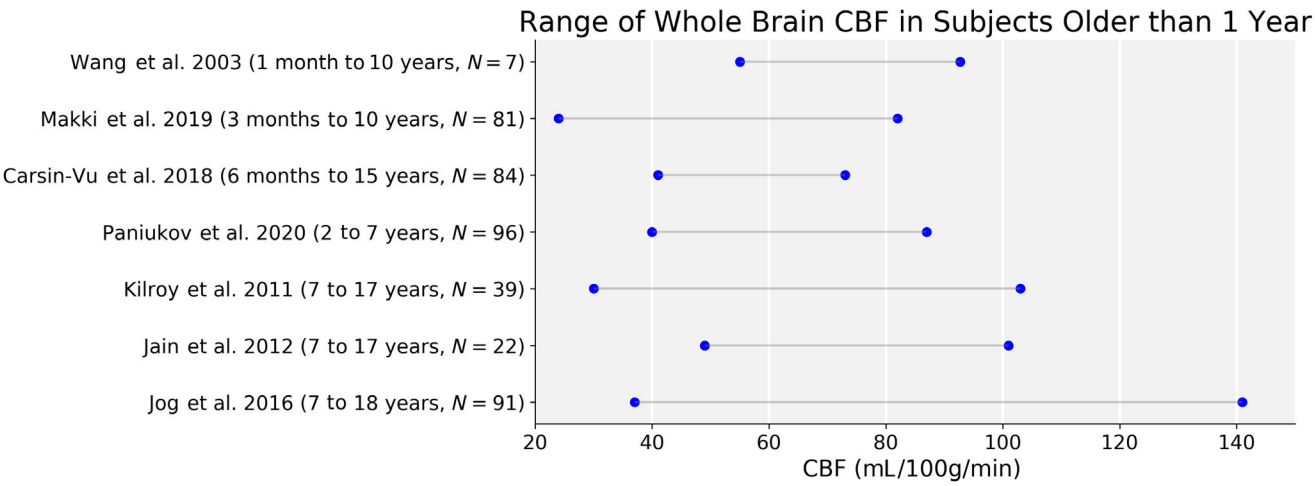

FIGURE 3: Distribution of mean whole brain CBF in subjects older than 1 year. Overall, the whole brain CBF in these studies is between 24 and 141 mL/100 g/min.

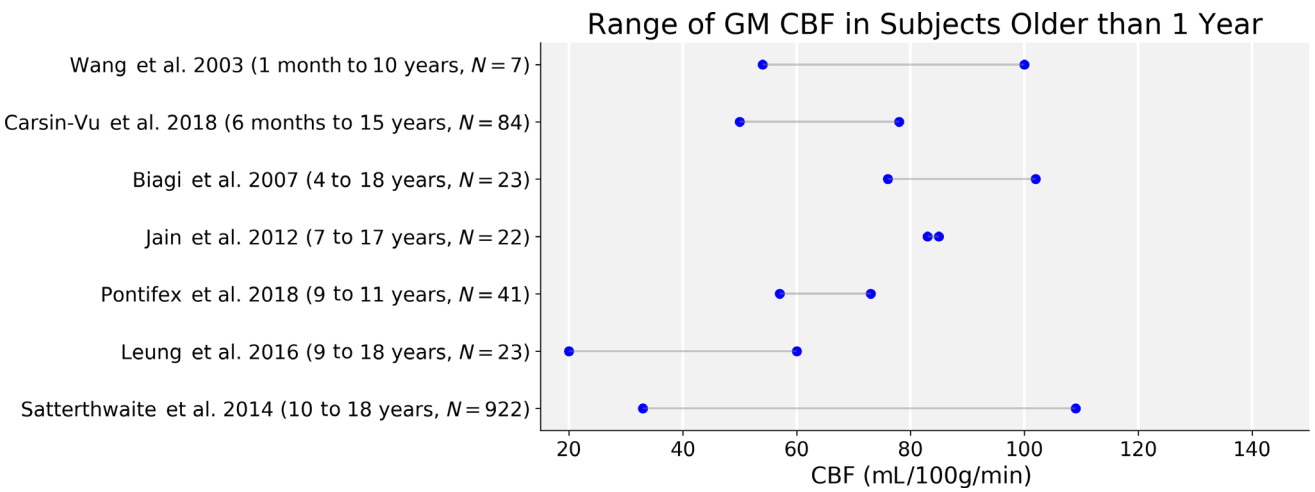

FIGURE 4: Distribution of mean GM CBF in subjects older than 1 year. Overall, the whole brain CBF in these studies is between 20 and 108 mL/100 g/min.

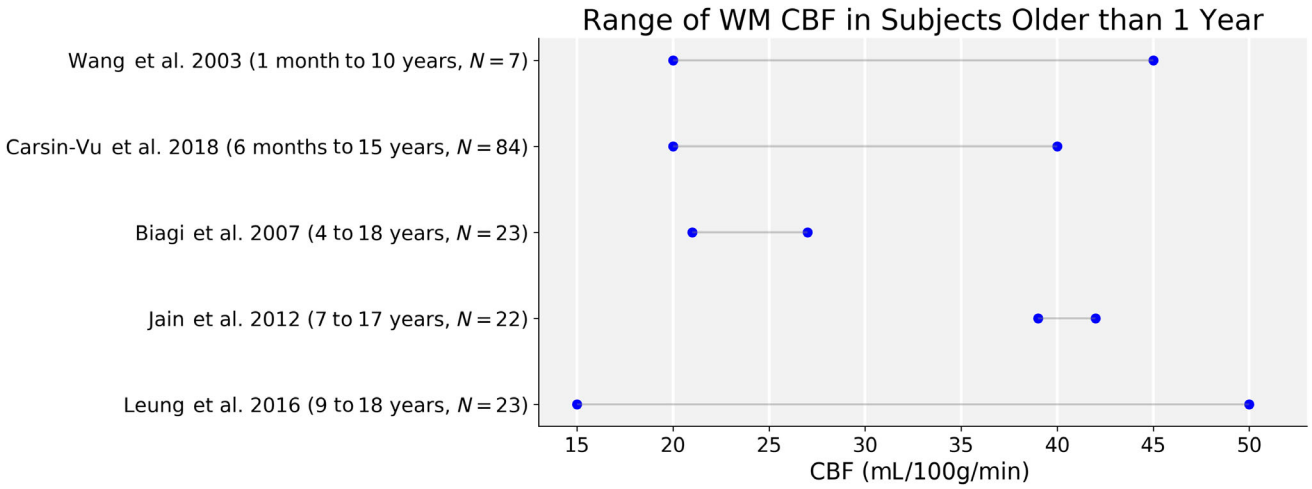

FIGURE 5: Distribution of mean WM CBF in subjects older than 1 year. Overall, the WM CBF in these studies is between 15 and 50 mL/100 g/min.

CBF Measurements in Children Younger Than 1 Year

Among the selected papers, seven studies investigated CBF in normal subjects younger than 1 year, as shown in Fig. 6. Among the three studies that reported whole brain CBF less than 5 days after birth, the range was between 4 and 23 mL/100 g/min. The whole brain CBF in four infants younger than 3 days was between 15 and 22 mL/100 g/min measured by the gold standard ^{15}O-water PET modality.[38] For the studies that reported age in gestational weeks, CBF of the whole brain appeared to be much higher—ranging from 17 to 90 mL/100 g/min in subjects aged between 34 and 114 gestational weeks.[37,40] Several studies included both full and early-term infants and demonstrated that CBF in pre-term infants was significantly lower than those born in full-term.[34,37,44] Regarding the factors affecting CBF in infants, only one study found that CBF (ranging between 17 and 90 mL/100 g/min) measured by PC MRI increased with age among infants between 34 and 114 gestational weeks at the time of scan.[37]

Discussion

In this work, we reviewed multiple studies that investigated CBF in healthy children using PET and MRI. This systematic review compared factors affecting CBF measurements such as age, gender, mood, and sedation. We identified 32 articles from 3 databases with a total of 2668 normal subjects. Among the factors affecting CBF measurements, the physiological factors associated with the experimental subject included age, gender, and use of recreational drugs; the technological factors associated with the design and implementation of the CBF measurements included: type of imaging modality and sedation. The primary findings of this paper were: 1) CBF increases with age after birth until pre-adolescent years and then declines; 2) CBF in males declines more rapidly after puberty than in females; 3) consuming cannabis increases regional CBF among teenagers of both genders; 4) CBF in pre-term infants is lower than the value in children born in full term.

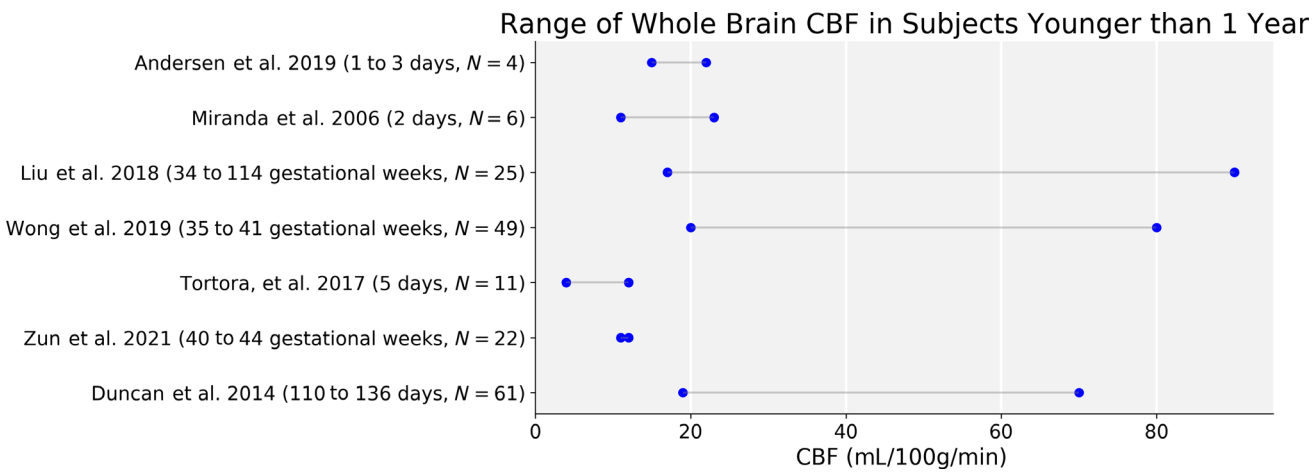

FIGURE 6: Distribution of mean GM CBF in subjects younger than 1 year. Overall, the whole brain CBF in these studies is between 4 and 90 mL/100 g/min.

Impact of Age on Pediatric CBF

Among all the studies reviewed, age was the most frequently considered physiological factor to demonstrate variation in CBF. Several studies revealed that pediatric CBF increases after birth and peaks at pre-adolescent age using ASL and PC MRI.[20,37,40,41] In a longitudinal study, Paniukov et al investigated the change in CBF measured at least 6 months apart in 96 children (50 males and 46 females) aged 2–7 years using single-delay ASL.[41] Results indicated a statistically significant positive linear relationship between CBF and age in such regions as the prefrontal, temporal, parietal, and occipital cortex. Although the study focused on CBF measurements only, the increase in CBF occurs in parallel with changes in brain tissue volume and function found in other studies.[46,47] Since substantial expansion in cortical surface and network connectivity occurs during early childhood, increases in CBF may reflect the growing demand for nutrients and enable the expected structural and functional changes. As the brain becomes mature during teenage years, CBF is shown to decrease steadily and then plateau in early adulthood.[16,30] Such changes in CBF also mirror the change in the cerebral metabolic rate of oxygen ($CMRO_2$), a metric reflecting neuronal functions and working memory.[4] These data suggest that the decline in cerebral oxidative metabolism and CBF in older children may be in response to changing working memory tasks. Another possible explanation is synaptic pruning occurring during adolescence and early adulthood where extra synapses are eliminated as a way of maintaining efficient brain function in normal developments of brain circuits, which alters CBF indirectly.[48] In addition to CBF in children older than 1 year, CBF in healthy infants born full-term was also included in this review. Since some of these studies included CBF values in pre-term infants, we have found that whole brain CBF in full-term infants was generally higher than those born pre-term measured by ASL and PC MRI.[34,37,39,44] Taken together, the CBF alterations between birth and early adulthood may reflect energy consumption during different stages of brain development, both structurally and cognitively.

Several studies attempted to model the relationship between CBF and age by fitting a function to the CBF-age pair data and evaluating the prediction error of such function. The cubic polynomial function was found to be the best fit model in two studies that investigated the whole brain CBF in children older than 6 months based on the Akaike information criterion (AIC).[19,40] In essence, AIC favors models with a lower number of parameters and discourages overfitting. Since the sample size of these two studies ($N = 84$ and 49) was relatively large, AIC was an acceptable metric to assess goodness of fit. However, a major limitation of this technique was that neither of these studies investigated the fitting errors of the selected functions when new data are presented. Thus, future studies should include a test dataset to examine the performance of the derived model for understanding the relationship between CBF and age.

Impact of Gender on Pediatric CBF

Although many studies have shown that CBF in adult females is generally higher than in males,[49–51] the same trend was less frequently observed in the pediatric population except for one study that compared the effect of partial volume correction on CBF in males and females.[23] Specifically, female subjects aged between 5 and 18 years showed significantly higher CBF (by 13%) measured by ASL than males in the bilateral medial regions of the parietal lobes while no regions in males were seen that show higher CBF than in females. However, it should be noted that results in this study were derived using the model-free method for QUASAR ASL (a type of multi-delay ASL), which has been shown to underestimate CBF due to the deconvolution method applied.[52] Another possible explanation is the differences in hematocrit between male and female participants, which could affect the T1 relaxation of the arterial blood during CBF quantification.[53] Other studies did not find significant differences in CBF between genders measured by ASL and/or PC MRI.[16,19,25] Puberty is a unique factor for variations in pediatric CBF, during which, according to one study, males and females demonstrate divergent trajectories in CBF with age.[28] In particular, CBF in such regions as the insula, thalamus, and precuneus declines steadily in both genders in early puberty but the trend deviated in mid-puberty, with CBF in females increasing slightly while it continued to decline in males until late adolescence.[28] This observation might explain the CBF differences in adult males and females. Given the limited and mixed accounts of CBF variations due to gender, it is inconclusive if gender is a determinant factor for pediatric CBF. Based on the data in the selected studies, a rule of thumb would be to consider gender differences only for investigating CBF in subjects during years of puberty.

Impact of Mood on Pediatric CBF

In this review, we identified three factors affecting the mood of individuals during CBF measurements including the use of cannabis, hunger, and satiety (food consumption). In the study performed by Jacobus et al, chronic marijuana consumption decreased CBF in the medial frontal gyrus and insula among 23 healthy teenagers of both genders aged between 16 and 18 years who had consumed marijuana for an average of 398.6 days prior to the study.[26] This observation contradicted previous beliefs that cannabis was considered a vasodilator due to its effect to reduce heart rate and blood pressure in animal studies.[54,55] Since the evidence in human subject studies is sparse, it remains unclear regarding the acute and long-term cerebrovascular effects of cannabis. In terms of the effect of hunger and satiety on CBF measured

by ASL, it was found that CBF in the insula reduced significantly by 4% after 6 hours of hunger but increased significantly in both insula and precuneus after satiety (meal consumption).[42] Since these regions are associated with satisfaction,[56] it is believed that satiety and/or the anticipation of an upcoming meal has a direct impact on CBF. Based on these studies, participants should avoid cannabis, long periods of fasting, or consuming a large meal before neuroimaging studies.

Impact of Sedation on Pediatric CBF

Among the two studies reviewed regarding sedation, different types of sedation and anesthesia were applied to pediatric subjects up to 12 years old. Makki et al compared the effect on CBF measured by PC and ASL MRI using propofol only and a combination of propofol and ketamine.[45] No significant CBF differences were found between subjects (between 4 and 12 years old) sedated by propofol only and those by both propofol and ketamine. Similarly, subjects sedated by propofol or halogen also showed no significant differences in CBF compared to those awake during the scan.[16] Based on these data, sedation type seems to have no impact on the whole brain CBF in the healthy pediatric population, but it should be noted that no studies were done that compared sedation to no sedation.

A previous study found that patients sedated by a combination of propofol and ketamine experienced significantly shorter recovery times and higher blood pressure,[57] but no significant differences in respiratory rate were found. Since CBF is affected by the change in end-tidal CO_2, monitoring respiratory rate and end-tidal CO_2 during pediatric neuroimaging scans may provide further evidence about the impact of sedation on pediatric CBF. Nevertheless, the selected studies in this review demonstrated that pediatric CBF is not significantly affected by using ketamine at induction, providing additional insights that the combining propofol and ketamine should be used to sedate pediatric patients to reduce motion artifacts during neuroimaging scans.

Impact of Brain Tissue Volume on Pediatric CBF

In a study that evaluated the impact of GM tissue volume change on CBF during normal brain development, the authors found that CBF increased with rapid GM volume growth among 100 healthy children aged between 4 months and 18 years.[32] These data implied that continuous growth ASL CBF measured by ASL during childhood and teenage years revealed a protracted period of structural and functional development in brain maturation. Additionally, the cerebral volume peaked at 14.5 years for males and 11.5 years for females while changes in subcortical gray matter volume showed regional heterogeneity between the two genders.

Impact of Exercise on Pediatric CBF

The effect of aerobic exercise on CBF was examined in two studies by Chaddock-Hayman et al and Pontifex et al,[31,36] but they drew different conclusions as to the impact of exercise on pediatric CBF. While one group found that aerobic fitness was linked with a higher hippocampal CBF in children between 7 and 9 years,[31] the other found no significant CBF change between active exercise (running on a treadmill) and active control (normal pace of walking on a treadmill) among healthy children aged between 9 and 11 years.[36] Since the effect of aerobic exercise on CBF remains unclear, it is recommended that a resting period should be included before CBF imaging studies to minimize the impact of different fitness levels among individuals.

Impact of Imaging Modality on Pediatric CBF

Only one of the selected studies reported whole brain CBF measured by 2D PC and single-delay ASL MRI[4] as part of the analysis as to the impact of age on CBF and $CMRO_2$.[4] The results obtained by these two modalities were fitted using linear regression to derive the following relationship $CBF_{PC} = 1.14 \times CBF_{ASL} - 0.19$, implying that CBF measured by PC was consistently higher than the values obtained by ASL in children aged between 7 and 18. Similar observations were reported in healthy adults where CBF of PC was consistently higher than that measured by pseudo-continuous ASL.[58] It should be noted that the CBF results may be affected by limitations of the imaging modalities. For example, The CBF quantification using PC depends on precise segmentation of the arteries and the measurement of the total brain tissue volume. The segmentation can be challenging due to non-laminar flow and an oblique angle of the scanning plane. CBF measured by ASL may be limited by variations in labeling efficiency due to different labeling techniques and abnormal hematocrit levels such as in patients with sickle cell disease.[59] Regarding comparisons between different ASL techniques (such as PASL, CASL, and PCASL), since none of the selected studies measured CBF in the same cohort using multiple ASL techniques, we were unable to compare the different CBF values measured by different techniques. Nevertheless, in a study that compared the reproducibility of CBF in a cohort of healthy young adults (19–29 years) measured by different ASL techniques, it was found that CASL-based methods (continuous and pseudo-continuous ASL) were more reproducible than PASL based method due to higher SNR (within-subject coefficients of variation = 3.5% vs. 7.5%).[60]

Advantages and Disadvantages of the Imaging Modalities Reviewed

The reported CBF values in this review were obtained using three major types of imaging techniques: ASL MRI, PC MRI, and ^{15}O-water PET; each modality has its advantages

and disadvantages. Whilst most studies applied ASL MRI due to its ability to map regional brain CBF non-invasively, CBF measurements have been shown to be affected by transit time artifacts.[61] A systematic study comparing the impact of different post-labeling delays is desired to identify the optimal pediatric ASL method. Although PC MRI allows whole brain CBF measurements, it relies on the careful selection of encoding velocities and precise segmentation of the ICAs and VAs for CBF quantification in different age groups. An open question is how these factors influence the reproducibility of CBF measurements using PC MRI. In this context, it is worth including PC MRI as part of neuroimaging protocols. Despite ^{15}O-water PET being considered the gold standard CBF modality, its application on the pediatric population is limited due to radiation (1.9 mSv in the study by Andersen et al)[1,2] and complexity in quantification. As the sensitivity of PET detector improves, however, a possible solution is combining PC MRI and low-dose ^{15}O-water PET for CBF quantification using simultaneous PET/MRI systems.

Limitations

Regarding the rigor of this review, since no clinical trials were included, the quality of the selected papers was not evaluated using critical appraisal tools to assess the reproducibility, importance, and applicability of clinical evidence. CBF measurements in infants have been challenging due to motion, posture, and other unexpected factors such as the need for feeding during scanning. The data captured in our review are limited because the conditions of infants during and after scans were not well documented. It is valuable to include questionnaires to develop optimal and comfortable imaging conditions for CBF in infants. Among all the studies reviewed, no attempts were made to evaluate the pediatric CBF measurements across multiple locations and the effect of data harmonization. Due to the paucity of multi-center studies, the versatility and consistency of the imaging protocols across different imaging centers have not been confirmed. To date, it is still unclear which neuroimaging modality and technique is best for measuring CBF in pediatrics. Although a larger number of studies have employed this approach, no direct comparison was made between different post-labeling delay times. Furthermore, there were several studies that adopted multi-delay ASL to measure pediatric CBF in this review. Although multi-delay ASL was less widely applied, there was no evidence in our selected studies that indicated whether single-delay or multi-delay should be the favorable technique. Therefore, it is inconclusive for us to recommend that we should limit ASL imaging studies and favor a single-delay approach. Additionally, blood T1 may affect the precise quantification of CBF using ASL. However, no studies involving normal pediatric subjects were found in this review. A rapid blood test measuring hematocrit levels may be performed before imaging sessions to investigate the impact of blood T1 on CBF. Other open questions include the sensitivity of CBF measurements to different vendors and protocols and whether the different neuroimaging methods applied to the same cohort are more or less favorable than each other for pediatric CBF measurements. These questions may be addressed in future studies using similar experimental designs as those in Human Connectome Project Lifespan Studies.[62–64]

Conclusions

Based on the physiological factors reviewed, pediatric CBF at resting state in normal physiological conditions should be measured without the influence of hunger, mood, and cannabis and considerations should be taken regarding age and gender. To minimize the impact due to technological factors, CBF should be obtained using similar scanning parameters on the same modality. Gestational age at birth should be considered in neonate CBF measurements. Future pediatric CBF studies should recognize these factors to minimize their impact. More systematic investigations are desired to evaluate rigorously other potential confounds such as sedation and cerebral maturity.

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Author Contributions

Moss Y. Zhao: Conceptualization, methodology, investigation, writing, funding acquisition. Elizabeth Tong: Conceptualization, investigation, resources. Rui Duarte Armindo: Methodology, data curation. Amanda Woodward: Methodology, data curation. Kristen W. Yeom: Supervision. Michael E. Moseley: Supervision. Greg Zaharchuk: Supervision, manuscript editing, funding acquisition.

Conflict of Interest

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Greg Zaharchuk received funding support through GE Healthcare and Bayer Healthcare and equity from Subtle Medical.

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