INVESTIGATION OF THE EFFECTS OF AGE ON CBF AND THE BOLD RESPONSE: AN ARTERIAL SPIN LABELING MRI STUDY OF THE MOTOR CORTEX

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Investigation of the Effects of Age on CBF and the BOLD Response:

An Arterial Spin Labeling MRI Study of the Motor Cortex

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DEDICATION

This thesis is dedicated to my incredible parents, George and Pam Orient. I owe all that I have and will accomplish to their steadfast love and support. Krisztina Paulay Orient, édesanyám, thank you for being my guardian angel and my guiding star.
ABSTRACT OF THE THESIS

Investigation of the Effects of Age on Cerebral Blood Flow and the BOLD Response: An Arterial Spin Labeling Study of the Motor Cortex

by

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Master of Arts in Psychology
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Cerebral blood flow (CBF) plays a central role in the blood oxygen level dependent (BOLD) signal measured by functional magnetic resonance imaging (fMRI). Yet, age-related changes in CBF and its relationship with the BOLD response have not been studied extensively in typically developing children. Historically, positron emission tomography (PET) and single photon emission computed tomography (SPECT) have been used to study CBF during development. PET and SPECT studies have found that CBF increases rapidly in the first years of life, is elevated in childhood, and declines to adult levels in adolescence. However, due to their invasiveness, PET and SPECT studies have been limited to clinical contexts and measurements of CBF either at rest or with sedation. In addition to developmental change in CBF, studies of exercise and brain function with children (cognitive, electrophysiological, and fMRI experiments) suggest that level of physical activity affects CBF. The primary aims of this thesis were to assess whether there are age-related changes in CBF and its relationship with the BOLD response during a functional task and whether there is a relationship between participants’ level of physical activity and CBF measurements. To do so, this project used a noninvasive MRI method, arterial spin labeling (ASL), to examine CBF during rest and functional activity in typically developing children. Further, this study used an ASL technique, Quantitative Imaging of Perfusion using a Single Subtraction (QUIPSS), which simultaneously collects CBF and BOLD-weighted images to directly examine the relationship between CBF and the BOLD response. Participants included 8-year-old children \( (n = 8) \), 12-year-old children \( (n = 10) \), and adults 22-28 years of age \( (n = 9) \). This experiment focused on CBF in the motor cortex where stimulation with a finger tapping task was predicted to elicit a robust CBF and BOLD response. CBF was measured during a resting state scan. From functional images acquired during the task, three measurements were derived: absolute CBF change, percent CBF change, and percent BOLD change. These measures were calculated as the absolute or percent change in signal between rest and peak activity. In addition, both participant and parent reports of participants’ physical activities six months prior to the scan were retrospectively obtained with a survey. Age group comparisons of the hemodynamic measures showed that 8-year-old children and 12-year-old children had significantly greater resting CBF levels than adults. There were no significant differences in resting CBF levels between 8-year-old children and 12-year-old children. Eight year olds had significantly greater absolute CBF change than adults. No significant age-related differences were observed for percent CBF and BOLD signal change. Analyses of the relationship between physical activity level and CBF showed that neither participant-reported nor parent-
reported amounts of activity were related to the hemodynamic measures. This result may be due to higher than expected activity levels across the sample. Lastly, the finding that CBF is higher in children compared to adults without a corresponding elevation in BOLD signal suggests that additional physiological mechanisms that are elevated in childhood may offset the high CBF and result in a stable BOLD effect.
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CHAPTER 1
INTRODUCTION

Cerebral blood flow (CBF) is a fundamental physiological process that has not been studied extensively in the developing brain. CBF is defined as the rate at which oxygenated blood is delivered to cerebral tissue. Studies that examine CBF during brain development have been conducted primarily with positron emission tomography (PET) and single photon emission computed tomography (SPECT) in clinical settings. Though limited in number, PET studies that examine CBF during development indicate higher CBF in childhood than adulthood (Chiron et al., 1992). However, relatively little additional information is known about CBF dynamics in the healthy developing brain. Researchers use functional magnetic resonance imaging (fMRI) to study patterns of functional activity in the brain. Specifically, blood oxygen level dependent (BOLD) fMRI is being used increasingly to study activity in the developing brain. The BOLD signal measured with fMRI depends upon multiple physiological mechanisms, including CBF. Thus, age-related changes in CBF may contribute to age-related changes in the BOLD response. However, this relationship remains largely unexplored in children.

The contribution of CBF to BOLD raises several questions. Importantly, understanding the normal course of developmental change in CBF is crucial. Additionally, age-related changes in CBF during development could have a confounding effect on the MRI signal measured in children. Since prior studies show that CBF is higher in childhood than in adulthood, and CBF is a contributing factor to the BOLD effect, it is possible that age-related differences in CBF affect the BOLD response in children. Specific to the current study, a child’s level of physical activity may also affect CBF and the BOLD response in development. The aims of the current study are to understand age and physical activity related differences in CBF and the dynamics of the contribution of CBF to the BOLD response.

Functional MRI detects changes in blood oxygenation associated with neural activity. The signal that is measured reflects changes in the state of blood oxygenation. During neural
activity, cerebral blood flow increases locally in the brain and delivers oxygenated hemoglobin in the blood stream. Oxygenated hemoglobin is weakly susceptible to magnetization effects (diamagnetic) and thus does not alter the active brain region’s magnetic field. Oxygen is extracted from the oxygenated hemoglobin during activation. The rate of extraction is less than the rate of oxygenation delivery to active regions. In the venous system, deoxygenated hemoglobin is highly susceptible to magnetization effects (diamagnetic) and thus alters the active brain region’s magnetic field. However, this disruptive noise is lessened by the presence of excess of oxygenated hemoglobin that passes from the arterial supply into the veins during neural activity. Due to the higher ratio of oxygenated to deoxygenated hemoglobin in the draining veins, the MRI signal increases, which is known as the BOLD effect. Thus, CBF makes an integral contribution to the BOLD response measured in fMRI.

Current knowledge regarding pediatric CBF rests largely on brain imaging studies conducted in a clinical context. Historically, PET and SPECT have been used for clinical diagnostic imaging purposes with children. PET and SPECT diagnostic scans of neurologically normal children have provided a basis for research reports on CBF during childhood. These studies have found increased CBF rates in children relative to adults (Barthel et al., 1997; Chiron et al., 1992; Takahashi, Shirane, Sato, & Yoshimoto, 1999). Further, PET and SPECT studies suggest an arch-shaped pattern of development in which CBF rises in infancy, peaks in childhood years, and declines to adult CBF levels in early adolescence (Chiron et al., 1992; Takahashi et al., 1999). One possible explanation for why CBF may be higher in children than adults is that increased synaptic density observed in childhood as well as ongoing myelination drive metabolic demands and require a greater supply of oxygen and nutrients from arterial blood than is needed in adulthood. Despite these findings, PET and SPECT have limitations. PET and SPECT involve injecting radioactive tracers into arterial blood to measure CBF. Due to their invasiveness, these methods are used solely for the purpose of clinical diagnosis in children. Another methodological issue is that these methods in a clinical context only examine resting state CBF and do not investigate the impact of functional activity on CBF while in the scanner. Arterial spin labeling (ASL), a more recent MRI-based imaging method, helps researchers surmount these methodological and safety limitations.
**ARTERIAL SPIN LABELING (ASL): A NONINVASIVE METHOD FOR CBF MEASUREMENT**

ASL is a noninvasive neuroimaging method that allows researchers to safely investigate changes in CBF in typically and atypically developing children during rest and activation. ASL applies a magnetic tag with an inversion pulse to arterial blood flowing into active brain regions. Both control (without the presence of blood) and tagged images are acquired in alternation within the same slice. CBF is measured as the difference between the control and tag images. BOLD is measured as the average between control and tag images. A method called Quantitative Imaging of Perfusion using a Single Subtraction (QUIPSS II) has been developed that enables simultaneous acquisition of both ASL and BOLD signal data during activity (Wong, Buxton, & Frank, 1997). Thus, ASL allows for CBF and BOLD data to be captured within a single set of brain images.

Few studies have used ASL to measure resting CBF rates in children. Wang et al. (2003) demonstrated the feasibility of using ASL with children and healthy adults during sedation in clinical settings. They found that mean resting CBF in children was 1.27 times higher than in adults. Biagi et al. (2007) used ASL to measure resting CBF in groups of children, teenagers, and adults. All children participated as part of a clinical diagnostic procedure. Biagi and colleagues found significantly higher CBF in children compared to adults. In addition, high resting CBF levels remained constant until age 10 to 12 years and then decreased rapidly to adult levels in early adolescence. Taki et al. (2011) found that typically developing children also show an arching trajectory of CBF (resting state) increase and decline across childhood.

To date, only one study has used QUIPSS II ASL to assess resting and active-state CBF in typically developing children. Moses, DiNino, Hernandez, and Liu (2013) found age-related differences in resting and activity-related CBF change during stimulation of the auditory cortex. Comparisons between age groups revealed that 8-year-old children had significantly greater resting CBF levels than 12-year-old children and adults. Building upon these findings, the current aims of the study were to examine whether there were age-dependent differences in CBF among typically developing children and whether the CBF and BOLD response to activation seen in the auditory cortex generalizes to a complementary brain region: the motor cortex.
Impact of Physical Activity on CBF in Children

Research has demonstrated that physical activity affects cognition, brain structure, and regional cerebral activation in children. Davis et al. (2011) investigated the relationship between exercise regimen manipulation and executive control skills. They found that pre-adolescent children in a high exercise dose condition had average planning (executive control) scores 3.8 points higher than pre-adolescent children in the low exercise condition. Physical activity was shown to have short-term effects on executive functioning in children. As an extension of the study, the research group hypothesized that regular vigorous physical activity promotes children’s development by affecting the brain systems that underlie cognition and behavior. In an fMRI component of their study, Davis and colleagues observed increased prefrontal cortex activity in children in the high exercise condition versus those in the low exercise condition. Thus, physical activity is related to regional brain activity and cognitive performance. Chaddock et al. (2010) examined the correlational relationship between physical activity level and anatomical brain development with MRI in pre-adolescent children. Chaddock and colleagues (2010) found that children with higher aerobic fitness levels had larger hippocampal volumes compared to less fit children. Chaddock et al. (2012) also tested the higher-order cognitive skills of children (ages 9 to 10 years) by having them complete a flanker task paradigm (an attentional matching/recognition task). During increased cognitive demands from the task, children with higher fitness levels showed greater activation in the prefrontal and parietal cortices than children with lower fitness levels.

Studies have also examined the impact of physical activity on brain function with electrophysiological event-related potentials (ERP) recordings. ERP measures detect electrophysiological signals after a person responds to a cognitive or sensory stimulus. Hillman, Castelli, and Buck (2005) investigated the relationship between fitness and ability to focus attention as measured by ERPs in young children. The researchers found that highly fit children had greater P3 (a brain wave exhibited during decision making) amplitude than less fit children, which was indicative of better attentional memory. Hillman, Buck, Themanson, Pontifex, and Castelli (2009) demonstrated that pre-adolescent children in an exercise condition had ERP signals that were indicative of better academic achievement (reading scores on a standardized testing measure) than a sedentary control condition. Furthermore, Pontifex et al.’s (2011) study of flanker task response accuracy (ERP response)
noted that children with higher fitness levels were able to maintain better response accuracy across cognitive stimuli than less fit children. Higher fitness children also had higher P3 amplitude suggesting greater capacity to modulate cognitive control. Therefore, evidence provided by previous researchers suggests that physical activity may alter electrophysiological response to various cognitive stimuli in children.

All of the mentioned studies have several limitations. These studies do not examine the fundamental aspects of CBF and BOLD in children. They do not explore the possibility that physical activity may impact CBF in children and thereby affect the hemodynamics of the BOLD response during neuroimaging. Conducting neuroimaging investigations like the proposed study will begin to investigate the possible relationship between physical activity on CBF and BOLD in children. Given the limited precedent for measuring CBF in children in relationship to their level of physical activity, the first step was a basic one of determining whether there is evidence of either higher or lower CBF in children who are regularly active compared to more sedentary children.

**AIMS OF CURRENT STUDY**

The primary objective of the current study was to determine whether or not there were differences in (1) resting state CBF, (2) stimulus-driven CBF in response to a simple motor finger tapping task, and (3) BOLD responses between three age groups of typically developing individuals, 8-year-old children, 12-year-old children, and adults. This thesis used QUIPSS II ASL data acquired prior to this project to determine whether or not there were age-related differences in CBF and BOLD responses.

Another objective of this thesis was to use the same dataset to determine whether or not there were differences in CBF and BOLD responses in children with respect to physical activity level. This study provided an opportunity to begin to explore possible correspondences between physical activity and cerebral blood flow during development. Understanding the role of physical activity in development may also serve public health initiatives regarding the benefits of regular physical activity in childhood. To address this aim, additional information was acquired retrospectively from participants in the ASL study, who had already been imaged, to assay their level of physical activity at the time that they participated in the imaging sessions. Child participants were then grouped into “relatively
high” and “relatively low” activity groups in order to assess the possible impact of physical activity level on their hemodynamic responses.

**HYPOTHESES**

Based on the previous findings of CBF and BOLD measurements in the auditory cortex of the three age groups, the following was hypothesized:

**Resting State CBF**

Children were expected to have greater resting state CBF than adults. Additionally, it was predicted that 8-year-old children would have greater resting CBF than 12-year-old children. Lastly, 12 year olds were not expected to have greater resting CBF than adults.

**Stimulus-Driven CBF and BOLD Responses**

Children were expected to have a greater absolute difference in CBF between resting state and stimulation than adults. Based on the previous study which focused on the auditory cortex, percent CBF change and percent BOLD change were predicted to be comparable across age groups.

**Activity Survey Hypothesis**

Differences in resting state CBF, absolute CBF change, and possibly in CBF and BOLD percent change were expected between children with “relatively high” and “relatively low” levels of physical activity.
CHAPTER 2

MATERIALS AND METHODS

ASL IMAGING PARTICIPANTS

Participants were a total of 27 individuals in three age groups: 8-year-old children ($M = 8.93$ years, $SD = 0.85$, $n = 8$, 1 male), 12-year-old children ($M = 12.31$ years, $SD = 0.87$, $n = 10$, 3 males), and adults ($M = 22.06$ years, $SD = 1.17$, $n = 9$, 4 males). These age groups represented different phases of developmental change in CBF based on PET and SPECT studies (Chiron et al., 1992; Takahashi et al., 1999; Wang et al., 2003) that suggest CBF rates are elevated at eight years of age and begin to decline to adulthood rates around 12 years of age. Additionally, children in this age range can remain still during image acquisition which made them ideal participants for this type of research.

Participants were recruited through advertising and local science fairs. Prior to participation, child participants provided written informed assent and their parents provided written informed consent as approved by the Institutional Review Boards of San Diego State University and the University of California, San Diego. Participants in the adult group also provided written consent. All participants were screened for sources of metal in their bodies prior to scanning. In addition, individuals with psychological or neurological conditions, learning disabilities, and those born more than 3 weeks premature were excluded from participation.

The study was designed to activate the primary motor cortex. In ASL imaging, the CBF signal has a lower signal to noise ratio than the BOLD signal. In order to study CBF and its relationship to the BOLD response in a functional paradigm, it is important to examine cortical regions where the CBF and BOLD signal are anticipated to be robust. Sensory and motor cortices are such regions and yield a reliable response to stimulation. The previous ASL study of functional CBF and BOLD examined the auditory cortex (Moses et al., 2013). The current aim of the study was to determine whether the results from that study generalize to the motor cortex.
**Motor Task**

The motor task consisted of a repetitive finger tapping sequence in which participants were instructed to respond to a serially ordered visual cue at a constant rate of one finger tap per second on an MRI-compatible response button box. The repetitive sequence was represented by numbering the fingers (1, 2, 3, and 4 with 1 being the index finger) on their dominant right hand and instructing participants to tap to a numerically ordered sequence on the response box. The visual cues were projected onto a screen at the foot of the MRI scanner and visible in a mirror positioned above the subject’s head in the scanner. Prior to scanning, participants were given a practice training session on a laptop to ensure familiarity with the task. The motor task was performed within a block design during MRI scanning. Each functional run began with 40 seconds of rest, after which 20 seconds of task and 40 seconds of rest were alternated for a total of 4 minutes 40 seconds in each functional run.

**Image Acquisition and Physiological Monitoring**

Images were acquired at the Center for Functional Magnetic Resonance Imaging (CFMRI) at the University of California, San Diego on a 3 Tesla General Electric Signa whole body system, with an 8 channel receiver-only head coil and a body transmit coil. Participants were provided with earplugs to reduce noise and were imaged without any form of sedation. Foam padding was placed around the individual’s head to decrease movement. Five 6 mm axial slices were positioned to encompass the motor cortex. The tagging band was a 100 mm thick slab positioned 10 mm inferior from the edge of the lowest imaging slice. Imaging parameters were as follows: repetition time (TR) = 2 s, inversion time (TI)1 = 600 ms, TI2 = 1500 ms, flip angle (θ) = 90°, field of view (FOV) = 24×24 cm², matrix size = 64×64, echo time (TE)1 =9.5 ms, TE2 = 30 ms.

Four functional runs (during which periods of task and rest were alternated) and a 3-minute resting state scan (parameters: TR = 2 s, TI1 = 600 ms, TI2 = 1500 ms, θ = 90°, FOV = 24×24 cm², matrix size = 64×64, TE1 = 9.5 ms, TE2 = 30 ms) was acquired for each participant. A cerebrospinal fluid (CSF) scan (parameters: TR = 4 s, TI1 = 700 ms, TI2 = 1400 ms, θ = 90°, (FOV) = 24×24 cm², matrix size = 64×64, TE1 =9.5 ms, TE2 = 50 ms) and a minimum contrast scan (parameters: TR = 2 s, TI1 = 700 ms, TI2 = 1400 ms, θ = 90°, FOV = 24×24 cm², matrix size = 64×64, TE1 =11 ms, TE2 = 50 ms) were acquired to calculate...
CBF in absolute units. A high resolution structural image was acquired using a 3D fast spoiled gradient (FSPGR) acquisition sequence with the following parameters: 1.0 mm slice thickness; TR = 7.6 ms, TE = 2.9 ms, TI = 450 ms, θ = 12°; FOV = 256x256 cm²; matrix = 25 x 25; NEX = 1.

Cardiac pulse and respiratory effort were recorded throughout the imaging sessions to reduce physiological noise and increase the signal to noise ratio in the ASL data (Restom, Behzadi, & Liu, 2006). A pulse oximeter (InVivo, Orlando, FL) was placed on the participant’s left index finger to record pulse rate. A respiration belt with an attached respiratory effort transducer (BIOPAC Systems, Goleta, CA) was placed around the participant’s chest to record respiratory effort. Participants were asked to refrain from consuming caffeine prior to taking part in imaging sessions since caffeine has been found to influence CBF change (Perthen, Lansing, Liau, Liu, & Buxton, 2008).

**ASL Data Analysis**

Data analyses were performed using Analysis of Functional NeuroImages (AFNI) software (Cox, 1996). Motion correction was implemented and physiological noise (heart rate and respiration) was regressed out. A quantitative measurement of CBF in units of ml/100ml/min was calculated from the 3-minute resting state scan in conjunction with the CSF and the minimum contrast scans. From each functional run, a CBF and BOLD time series were derived. The CBF time series was generated from difference of the activity-driven control and tag images. The BOLD time series was generated from the average of the control and tag images. For each subject, two CBF and BOLD time series were concatenated, respectively. CBF and BOLD time series were analyzed with a multiple regression model using 3dDeconvolve. The motor stimulus function was the regressor of interest, with six motion parameters. Baseline signal and linear trends were considered nuisance regressors. To correct for multiple comparisons, a simulation that estimated a cluster volume threshold with a voxel-wise and cluster-wise probability of \( p \leq .05 \) was generated. Clusters that met this criterion were retained for further statistical analyses.

**Region of Interest (ROI) Analysis**

ASL images were co-registered with high resolution structural images for localization of the task-related CBF and BOLD changes. CBF and BOLD responses were assessed in the
left motor cortex corresponding to the dominant right hand in all subjects. The primary motor
cortex ROI was manually drawn on the high-resolution anatomical images in the axial plane.
The ROI included the precentral and postcentral gyri in the left hemisphere. The ROI was
traced on five slices starting at the fundus of the central sulcus in the location of the omega-
like form of the precentral gyrus in the axial plane at the most inferior slice. For voxels
within the ROI that met or exceeded the statistical thresholds described above, the four
cycles of task and rest within the run were averaged to create single mean CBF and BOLD
time series for each participant. From these time series, multiple indices were derived. Within
each individual, resting state CBF, absolute change in CBF, percent difference of CBF, and
percent signal change for BOLD were measured. Absolute CBF change was calculated as the
difference between the average signal value during the initial rest period and the average
signal value during the time of peak response during activity, which was 7-13 TRs after the
onset of the stimulus to allow for hemodynamic rise time. Percent CBF change and the
percent BOLD signal change were calculated as the percent change in signal between rest
and peak. Separate one-way ANOVA tests were performed to test for age group differences
between resting CBF, absolute CBF change, percent CBF change, and percent BOLD signal
change. Differences between the means of individual age groups were tested with least
significant differences (LSD) tests.

**Physical Activity Survey Participants**

Participants in the physical activity survey were individuals who had previously
participated in an ASL imaging session (5 eight-year-old children, 8 twelve-year-old
children, and ten adults). The families of children who participated in motor brain imaging
sessions were contacted retrospectively by telephone to invite them to participate in the
survey and later to obtain information (informed consent as approved by the Institutional
Review Boards of San Diego State University and the University of California, San Diego)
about the participant’s physical activity at the time of his or her participation in the imaging
session. In order to have a sufficient sample size, the parents of participants in the previous
study of the auditory cortex were also contacted. The survey was administered to all
participants (child and adult) and to a parent of participating children.
The survey was designed to inventory participants’ activity in order to estimate the number of hours they engaged in weekly physical activity and to obtain complementary information as indicators of activity and fitness levels. The estimated hours of physical activity served as a basis for identifying relatively high and low activity level sub-groups. The survey questions were selected and adapted from the adult and student surveys that were part of James Sallis’ Amherst Health & Activity Study (Sallis, n.d.a, n.d.b). Questions included queries about the method of transportation a child used to go to school, how many hours per week a child played a sport, the child’s level of physical activity in comparison to those of the same age and sex, how often the child went to the nearest public park to play, and how often the child regularly partook in physical activity (see Appendix).

**Physical Activity Survey Analysis**

Based upon the itemized questions from the physical activity survey, hours of participant-reported activity and parent-reported activity were collected. Once the survey was completed, the number of hours of physical activity per week were summed by the experimenter. The total number of participant-reported and parent-reported hours were then analyzed. It is important to note that participants reported the hours per week of multiple different activities without summing those hours themselves, which may have led to an over-report of the total number of active hours. The activity data from two subjects (one motor task and one auditory task participant) were excluded from the group analyses due to an unusually high number of hours of activity reported by the parent (25 hours for motor, 27.5 hours for auditory) and the child (31 hours for motor, 27.5 hours for auditory). For a third motor participant, the child’s reported activity was not included in the analysis due to the subject being off-task during the survey administration. For statistical analyses, participant-reported and parent-reported activity was correlated (partial correlation) with each of the four hemodynamic measures separately, with age as a covariate. Task (motor, auditory) was also a covariate for stimulus-driven hemodynamic measures. Overall, children ($M = 13.38$ hours per week, $SD = 4.0$) and adults ($M = 7.28$ hours per week, $SD = 3.61$) reported a greater number of hours of physical activity than the minimum recommended hours per week (7 hours) by the Centers for Disease Control and Prevention (2014) (Figure 1).
Figure 1. (A) Participant-reported hours of physical activity as a function of age in years. (B) Parent-reported hours of physical activity as a function of age in years. The green and orange dashed lines represent the recommended hours of activity per week for children (7 hours) and adults (2.5 hours), respectively.

As a result, there were no subjects with a low level of physical activity as defined by Centers for Disease Control and Prevention. Consequently, participants in the lower 33% of the distribution constituted a “relatively low” activity group who were active less than 13 hours per week ($n = 4$) and those in the upper 33% constituted a “relatively high” activity group who were active for more than 15 hours per week ($n = 4$) for comparisons. Each of the hemodynamic measures were compared between the “relatively low” and “relatively high” activity groups for differences with a set of ANCOVA tests.

Activity preference was another factor of interest included in the survey. A survey item asked what type of activities the participant typically participated in during their recreational time. This provided a complementary and qualitative indicator of their activity level. The item was as follows: In the 6 months leading up to the scan did you/your son or daughter: (A) Almost always choose activities like TV, reading, listening to music, or computers. (B) Usually always choose activities like TV, reading, listening to music, or computers. (C) Just as likely to choose activities as recreation. (D) Usually choose activities like bicycling, dancing, outdoor games, or sport, or (E) Almost always choose activities like bicycling, dancing, outdoor games, or sports. Answers were ranked from 1-5, corresponding to answers A through E, respectively. These rankings were then correlated with the hemodynamic measures and BMI. Spearman’s Rho ranked correlations were utilized to test for these possible relationships. Both parent and participant activity preference were recorded to account for possible under- or over-estimation of participant activity preference.
Body Mass Index (BMI) was assessed for both adult and child participants based upon a question within the survey that inquired about height and weight at the time of the imaging scan session. For adults and children, BMI was calculated by dividing weight in pounds by height in inches squared (Centers for Disease Control and Prevention, 2014). One imaging subject did not report their height and weight at the time of survey administration and thus was excluded from the BMI analyses. BMI was correlated with the resting and stimulus-driven hemodynamic measures, reported activity hours, and physical activity level.
CHAPTER 3

RESULTS

RESTING STATE CBF

A one-way ANOVA revealed a main effect of age group on resting CBF, $F(2, 24) = 8.14, p = .002$. Least significant difference (LSD) post-hoc analyses were conducted to test for differences between individual age groups. Eight-year-old children ($M = 66.80$ ml/100ml/min, $SE = 4.02$) had significantly greater resting CBF levels than adults ($M = 49.45$ ml/100/ml/min, $SE = 2.33$), $p < .001$. Additionally, 12-year-old children ($M = 59.49$ ml/100 ml/min, $SE = 2.14$) had significantly greater resting CBF levels than adults, $p = .033$. There were no significant differences between 8-year-old children and 12-year-old children, $p = .065$. Figure 2 illustrates the mean resting CBF levels for each age group.

![Figure 2. Mean resting state CBF values for each age group. The vertical bars represent the standard error of the mean.](image)

STIMULUS-DRIVEN CBF AND BOLD RESPONSES

Absolute change in CBF significantly differed based on age group, $F(2,24) = 4.61, p = .020$. LSD tests showed that eight-year-old children ($M = 45.80, SE = 5.88$) had
significantly greater absolute CBF change than adults \( (M = 24.49, SE = 4.37) \), \( p = .006 \).

Twelve-year-old children did not differ significantly from eight-year-old children \( (p = .12) \) or adults \( (p = .14) \). Figure 3 illustrates the average time series of absolute change in CBF for each age group. The black bar indicates the stimulus onset and the blue bar indicates the time points defined as the peak (7-13 TRs after the onset of the stimulus).

![Figure 3. Mean time series of absolute CBF change for each age group. Eight-year-old children demonstrated a greater increase in absolute CBF change than adults. The vertical bars represent the standard error of the mean.](image)

A one-way ANOVA revealed no significant differences between age groups for percent CBF change, \( F(2, 24) = 0.021, p = .979 \), \( (Ms = 22.06, 21.52, 21.22 \) for 8-year-old children, 12-year-old children, and adults, respectively). Figure 4 presents the average time series of percent change in CBF for each age group. No significant differences were found among age groups for percent of BOLD signal change, \( F(2, 24) = 0.355, p = .705 \) \( (Ms = .33, .33, .39 \) for 8-year-old children, 12-year-old children, and adults, respectively). Figure 5 presents the average time series for percent BOLD signal change for each age group.
Figure 4. Mean time series of percent CBF change for each age group. The vertical bars represent the standard error of the mean.

Figure 5. Mean time series of percent change in BOLD signal for each age group. The vertical bars represent the standard error of the mean.
**PARTICIPANT-REPORTED AND PARENT-REPORTED HOURS OF PHYSICAL ACTIVITY**

To test the relationship between participants’ reported hours of physical activity and each of the four hemodynamic measures, partial correlation analyses were performed with age as a covariate. A comparable set of analyses examined the relationship between the parents’ report of their child’s activity and the hemodynamic measures. Since the survey data included responses from participants in both the motor and auditory tasks and the tasks elicit different magnitudes of functional signal change, it was necessary to control for task differences in addition to age in the analysis of the functional data.

The correlation analysis of participant-reported activity and resting state CBF did not show a significant relationship between the two, $r(18) = -.257, p = .288$. Similarly, absolute CBF change and participant-reported activity were not significantly correlated, $r(17) = .047, p = .854$. Again, no relationship was found between participant-reported activity and percent CBF change, $r(17) = .212, p = .398$. Participant-reported activity and percent BOLD change were significantly correlated, $r(17) = .650, p = .004$. This statistic remained significant after removal of one participant from the sample who exhibited a negative percent BOLD change. For parent-reported hours of activity, no systematic relationship was found with resting state CBF, $r(18) = -.224, p = .342$, nor was there a relationship with absolute CBF change, $r(17) = .043, p = .863$, or percent CBF change, $r(17) = .082, p = .739$. Parent-reported activity and percent BOLD change were significantly correlated, $r(17) = .544, p = .016$. This finding also remained significant after removal of the previously mentioned outlier. Figure 6 (A-D) and Figure 7 (E-H) illustrate the correlations between the hemodynamic measures and participant-reported or parent-reported hours of activity, respectively.

**HIGH AND LOW ACTIVITY LEVEL GROUP COMPARISONS**

The relationship between physical activity level and the hemodynamic measures were tested with an ANCOVA with age as the covariate. For stimulus-driven measures, task type was added as a covariate. Analysis revealed no significant effect of physical activity level on resting state CBF, $F(1, 4) = 0.016, p = .904, \eta_p^2 = .003$. There was no significant effect of physical activity level on absolute CBF change, $F(1, 4) = 0.124, p = .742, \eta_p^2 = .030$. There was no significant effect of physical activity level on percent CBF change, $F(1, 4) = 1.24, p = .334, \eta_p^2 = .231$, or on percent BOLD change, $F(1, 4) = 0.817, p = .417, \eta_p^2 = .170$. 


Figure 6. Participant-reported hours in relation to hemodynamic measures. (A) Hours of activity as a function of resting state CBF. (B) Hours of activity as a function of absolute CBF change. (C) Hours of activity as a function of percent CBF change. (D) Hours of activity as a function of percent BOLD signal change.

**BODY MASS INDEX (BMI)**

The relationship between BMI and participant-reported activity or parent-reported activity was tested with a correlation analysis with age as a covariate. Analyses revealed no significant relationship between BMI and participant-reported hours of activity, $r(17) = -0.273, p = .272$, or parent-reported hours of activity, $r(17) = -0.104, p = .671$. Similarly, there was no significant correlation between BMI and resting state CBF, $r(17) = .167, p = .495$.

For stimulus-driven CBF and BOLD analyses, age and task type were included as covariates. Body mass index was significantly correlated with absolute CBF change, $r(16) = -0.483, p = .042$. Figure 8 illustrates the negative correlation between body mass index and absolute CBF change. This statistic remained significant after the removal of one participant whose BMI value was 33.30 ($p = 0.017$). Body mass index was not significantly related to percent change of CBF, $r(16) = -0.343, p = .163$, or percent change of BOLD signal, $r(16) = -0.042, p = .867$. 
Lastly, an ANCOVA revealed no effect of level of physical activity on BMI, \( F(1, 4) = .587 \) \( p = .486 \), \( \eta_p^2 = .128 \), when controlling for age.

**Activity Preference**

There was a marginally significant negative correlation between participant-reported activity preference and resting state CBF, \( r_s(19) = - .440 \), \( p = .046 \). No significant relationships were revealed between participant-reported activity preference and absolute CBF, \( r_s(19) = - .002 \), \( p = .993 \), percent change CBF, \( r_s(19) = .061 \), \( p = .792 \), or percent change of BOLD signal, \( r_s(19) = .022 \), \( p = .924 \). No significant correlations were observed between parent-reported activity preference and any of the four hemodynamic measures of resting CBF, absolute change in CBF, percent change in CBF, or percent change of the BOLD signal \( (r_s = -.275, .190, .265, .121, \text{ and } ps = .227, .411, .245, .600, \text{ respectively}) \).
Figure 8. Body mass index as a function of absolute CBF change.
CHAPTER 4

DISCUSSION

CEREBRAL BLOOD FLOW DURING DEVELOPMENT

This project investigated potential age-related changes in measures of CBF and the BOLD response. This study demonstrated significant age-related differences in CBF in typically developing children. Specifically, children had greater resting CBF levels than adults. There were also age-related differences in stimulus-driven CBF measures. Eight-year-old children had significantly higher rates of absolute CBF change than adults and 12-year-old children. Yet, there were no significant age-related differences for percent change of CBF or percent BOLD signal change.

Previous studies have suggested that CBF is elevated in childhood and that CBF decreases to adult levels in adolescence (Barthel et al., 1997; Chiron et al., 1992; Ogawa, Sakurai, Kayama, & Yoshimoto, 1989; Takahashi et al., 1999). Barthel and colleagues’ (1997) SPECT study found that CBF decreases during development in children 4 to 15 years of age. Chiron and colleagues showed that CBF increased until 5 to 6 years of age before declining to adult levels between 15 to 19 years of age. Ogawa et al.’s (1989) group found that children’s CBF approaches adult levels by 10 years of age. Takahashi and colleagues (1999) found that CBF increased significantly during childhood and peaked at approximately 7 years of age. In our study, 8-year-old children had higher rates of resting CBF levels and absolute CBF change than adults. These results concur with the previous studies that show CBF increases in early years, peaks in childhood, and declines to adult levels in adolescence.

Few studies have used ASL to study developmental change in cerebral blood flow during childhood. Those that have, examined resting state CBF. Biagi and colleagues (2007) conducted a large age-span study (participants’ age ranged from 4 to 78 years of age) in which they found that CBF values declined as age increased. Furthermore, they noted that CBF remained constant up until shortly after 10 years of age. After this age, CBF sharply declined. Wang and colleagues (2003) found that children exhibited a 30% increase in absolute cerebral blood flow in comparison to adults. Lastly, a study by Taki et al. (2011)
found that CBF development in children follows an arching trajectory similar to the one proposed by Chiron and colleagues (1992).

One previous study has used ASL in a functional paradigm to probe the relationship between CBF and BOLD in school age children (Moses et al., 2013). This study of cerebral blood flow and BOLD in the auditory cortex revealed that 8-year-olds had higher resting CBF than 12-year-old children or adults. Children had also shown a greater rate of absolute CBF than adults. Overall, the results of the present study are in accordance with previous ASL findings in regard to the hemodynamic response to stimulation in the developing brain. Importantly, the current study suggests that the previous findings are not limited to auditory cortices and that they may generalize across the cortex.

**CBF AND THE BOLD RESPONSE**

It is important to note that several other processes of brain development follow similar developmental trajectories as CBF. Synaptic density (Chugani, 1998) and gray matter development (Wilke, Krägeloh-Mann, & Holland, 2007) are examples of aspects of brain development that show overgrowth followed by pruning. It is thought that in order for the brain to manage rapid growth, metabolism and oxygenation also need to increase, in addition to increased cerebral blood flow. In a PET study conducted by Chugani, Phelps, and Mazziotta (1987), local cerebral metabolic rates for glucose (1CMRGlc) in children 3 to 4 years of age exceeded that of adults. Cerebral metabolic rate for oxygen (rCMRO₂) in children also showed a similar effect (Takahashi et al., 1999). Although CBF in the current study was elevated in children in comparison to the adults and the absolute amount of CBF change from rest to activation was greater in the younger children, the BOLD response remained comparable between children and adults. These results suggest that processes which are upregulated along with CBF may play a role in the stability of the percent BOLD signal change between age groups. During neuronal activation, CBF and oxygenated blood to the brain increases. Oxygen is then extracted from oxyhemoglobin during activation. However, the rate of extraction is less than the delivery rate. Thus, excess oxyhemoglobin enters into the venous system where an increase in the ratio of oxyhemoglobin to deoxyhemoglobin generates the BOLD response. If an elevated resting state CBF and stimulus-driven CBF response is accompanied by an upregulation of metabolism and oxygen...
extraction, then the ratio of oxygenated to deoxygenated blood in the venous system would remain constant. In sum, the state of the additional physiological processes during development in childhood may account for the finding that the BOLD response remains unchanged as CBF increases in young children.

**Cerebral Blood Flow and Physical Activity**

This study’s investigation of children’s physical activity level in relation to hemodynamic measures was designed to better understand the mechanisms that may underlie changes in BOLD activity patterns previously reported in children with different levels of physical fitness or activity level. This project examined participants’ and parents’ reported physical activity behaviors in multiple ways. First, a possible link between amount of physical activity and CBF was tested with correlation analyses. Interestingly, there was a significant positive relationship between percent of BOLD change and participant-reported activity and parent-reported activity. An increase in the ratio of oxygenated to deoxygenated blood may account for this finding. An increase in the BOLD signal would occur when that ratio is increased further. It may be the case that individuals with high levels of physical activity extract less oxygen relative to increases in CBF during stimulation, which would enhance the magnitude of the BOLD response.

In addition to a correlational analysis approach, we also divided the participants into two groups based on the number of reported hours of activity. The goal of doing so was to directly compare a sub-set of participants who were in the lower 33% of the distribution of hours of activity with a sub-set of participants in the upper 33%. This was a complementary approach to correlational testing. Analyses showed an absence of a significant effect of physical activity level on resting state CBF, absolute CBF change, percent CBF change, or percent change in BOLD signal.

Supplementary information such as body mass index (BMI) was collected. BMI has been shown to be an indicator of fitness in adults and in children (Centers for Disease Control and Prevention, 2014). Specifically, those who have lower BMI values tend to be more fit than those who have higher BMI values. An adult with a BMI value between 18.5 and 24.9 is considered to be of “normal” weight. Interestingly, the BMI values that were calculated for the adult participants in the study were consistently within the normal range.
despite relatively low reported hours of physical activity (7.28 hours per week on average). One possible reason for this was that many participants had trouble recalling their exact height and weight at the time of their scan. Thus, the BMI values that were recorded were estimates and may not be entirely representative.

Collapsed across age groups (children and adults), BMI was negatively correlated with absolute CBF change. However, BMI was not correlated with any of the other three hemodynamic measures or with reported hours of physical activity. Previous evidence suggests that cerebral blood flow is negatively correlated with BMI values in adults. In a SPECT study involving healthy and overweight adults (measured by BMI), those with higher BMI values exhibited decreased regional CBF in the prefrontal cortex as well as the precentral and postcentral gyri (Willeumier, Taylor, & Amen, 2011). Furthermore, cerebral blood flow velocity was found to be negatively correlated with BMI in adult subjects who participated in a transcranial Doppler study (Selim, Jones, Novak, Zhao, & Novak, 2008). Within the same study, cerebrovascular resistance (blood pressure value divided by CBF velocity value) was found to be positively correlated with BMI. Although these studies solely investigated the relationship between BMI and cerebral blood flow in adults, the findings may very well extrapolate to children. One reason that the correlation may be evident for the measure of absolute CBF change between resting state and finger tapping and not for resting state CBF is that variations in CBF with BMI may only emerge when functional demands are placed on the system.

The survey included a more qualitative question that asked about a subject’s preference between physical activities and more sedentary activities in their recreational time. Although this question does not inventory a participant’s sedentary time as a complement to their activity, it begins to explore that dimension of behavior. Analyses of these data were used in addition to the quantitative measure of hours of physical activity as a convergent measure of physical activity. There was a marginally significant negative correlation between participant-reported activity preference and resting state CBF but not for any of the other hemodynamic measures. No significant correlations were observed between parent-reported activity preference and resting state CBF, absolute CBF change, percent change of CBF, or percent of BOLD signal change.
Another framework for assessing physical activity is to evaluate the number of hours that someone has engaged in sedentary behavior. The survey included a question about how much time a person participated on a weekly basis in different sedentary behaviors. Approximately half of the subjects, 11 out of the 21, directly declined or were resistant to respond. Their hesitation suggests that subjects may have been uncomfortable with the question and possibly their sedentary behaviors. While there is not sufficient data to analyze statistically, this may be an important point for consideration in a subsequent study. Additionally, quantifying sedentary hours provides an informal check on the plausibility of their reported number of hours of exercise.

The lack of a systematic relationship between physical activity measures and CBF in the multiple different analyses is somewhat unexpected because previous studies suggest that greater amounts of physical activity will result in higher CBF. Animal and adult human studies provide evidence of increased vasculature caused by exercise. Kleim, Cooper, and VandenBerg (2002) revealed that rodents with access to a running wheel for exercise increased vascularization in the motor cortex. Swain et al. (2003) similarly found angiogenesis in rats and increased CBF in the motor cortex. Thus, exercise triggers angiogenesis and vascular elaboration in associated CBF. A few human studies have also shown similar findings. For example, a study with adults who participated in a 3-month exercise intervention demonstrated increased cerebral blood volume (Pereira et al., 2007). In aging adults, a 4-month exercise program revealed higher resting CBF measures in the hippocampus than controls (Burdette et al., 2010).

There are multiple factors that may have masked possible correspondences between physical activity and hemodynamics in the brain in the current study. First, the sample was very physically active overall. The guidelines for physical activity are 60-minutes per day for children and at least 2.5 hours per week of moderate-intensity aerobic activity for adults (Centers for Disease Control and Prevention, 2014). Four 8-year-old children, seven 12-year-old children and eight adults (19 out of the 23 original survey subjects) exercised at these levels or above. Second, another possible factor that may have contributed to our findings is the fact that the hours of physical activity were summed up by the experimenter for use in analysis. The sum or composite amount of hours may be an overestimate of true activity because these subjects most likely did not take into account how the number of hours
reported for multiple different activities were adding up toward a weekly total. Third, subjects may have exhibited social desirability bias and over-reported the number of hours that they participated in a certain activity.

Further, in response to the results, this thesis examined whether an estimation of the hours of vigorous activity may be more closely related to CBF than those who participated in low effort activity. In a post hoc follow up, the experimenter attempted to divide activities listed in the survey into moderate and vigorous types to determine whether or not there was an effect of the degree of physical activity on CBF. Overall, most items on the list were not easily differentiated in that dimension. After closer inspection, most of the items were vigorous activity items as opposed to low-impact types of activities. This may suggest that administering a survey in the future with an ample distribution of categorically distinct (less strenuous versus more strenuous) physical activity items would be beneficial for understanding whether the degree of physical activity may have an impact on CBF.

With respect to the physical activity survey, were able to pilot and examine whether or not there is a relationship between CBF and physical activity. It is important to note the exploratory nature of the physical activity survey analyses and that there are limitations to acknowledge in administering a retrospective activity survey. Additional factors that may have played a role in our investigation of physical activity and hemodynamics are related to our specific sample and the limits inherent in retrospective studies. First, most of our subjects were active for more hours than expected across age groups. Thus, grouping subjects into high and low physical activity groups proved to be a challenge. Although this thesis originally intended to compare sedentary and active groups, our comparison of the top third and lower third of the distribution of hours of activity resulted in a comparison of two relatively active groups. Second, families consistently reported multiple activities associated with lessons and organized sports. Physical education classes during the school year contributed to the higher than expected level of physical activity from child participants. Maintaining a strict gym regimen during the work week and participating in recreational sports on the weekends was not uncommon for adult subjects. Lastly, attrition due to subjects changing residencies or not updating their contact information since the imaging sessions was a limitation to this project.
Although this study did not directly collect socioeconomic measures, socioeconomic status may have contributed to the profile of our results. In our sample, children had regular access to resources for physical activity. Not all physical education programs in school afford children moderate to vigorous activity (Cawley, Meyerhoefer, & Newhouse, 2007), but children in our sample reported these activities during their school program. Thus, families in our sample may have had a relatively high socioeconomic status and the sample appears to have been fairly homogenous in this regard. As a result, our group may not be representative of children in the San Diego region more generally.

Another possible limitation was that the experimenter asked participants about their activity during the 6-month period prior to the scan. Evidence from adult monkeys (Rhyu et al., 2010) suggests that within an interval of 12 weeks (3 months), the effects of exercise on CBF can return to baseline. It is possible that of the 6 months before the scan, subjects were not highly active in the three months immediately preceding the scan. Thus, possible enhancement of the vasculature due to the physical activity could have waned by the time of imaging. Whether the study by Rhyu and colleagues generalizes to the human developing brain is uncertain.

**Future Directions**

The research questions and findings in the current project merit attention in future studies that incorporate additional design features. One suggestion for future research would be to utilize a larger sample size and one that reflects the demographics of the San Diego community. Studying the development of CBF across a wider age band and multiple age groups within the band would be beneficial. Further, investigating whether the results from this study extend to other areas of the brain such as other sensory areas or higher order regions would be valuable. While the present study obtained behavioral information retrospectively as indices of fitness, a more precise, physiologically-based measurement of fitness such as maximal oxygen uptake testing would be recommended. Similarly, converging anatomical assessment measures in addition to BMI, such as skinfold thickness or waist-to-hip ratio, would provide a more comprehensive measure of fitness. Ideally, a future ASL study would compare children who have been assessed and identified as sedentary with lower fitness levels to children who engage in moderate to vigorous activity.
and demonstrate high levels of fitness. An intervention study in which sedentary children are examined before and after a physical activity intervention program would be the gold standard for testing the direct effect of exercise on cerebrovascular dynamics.
CHAPTER 5

CONCLUSION

This thesis demonstrated age-related differences in CBF at rest and during activity. Furthermore, it investigated the relationship between CBF and the BOLD signal response in children. Resting CBF was found to be higher in children than adults. Despite children having elevated resting CBF and absolute change CBF, percent change CBF and BOLD remained similar between age groups. This finding suggests that additional physiological mechanisms that are known to be elevated in childhood may play a role in offsetting CBF and result in a stable BOLD signal. This thesis also demonstrated that the findings that were originally observed in the auditory cortex in response to auditory stimulation generalize to the motor cortex and may be a property of hemodynamics across the cerebrum.

This project also evaluated CBF and hemodynamic measures in conjunction with the activity levels of children and adult participants. This study revealed positive correlations between physical activity and the BOLD response as well as a negative correlation between absolute CBF change and BMI. Given the limitations of our retrospective approach, it remains possible that additional correspondences exist between exercise and CBF, but were not detected here. Thus, ongoing research to systematically investigate physical activity levels in children and their effect on the delivery of blood and their contribution to the BOLD signal will be important for understanding the role that physical activity may play in healthy brain development.
REFERENCES


APPENDIX

PHYSICAL ACTIVITY SURVEY
Physical Activity Survey (Parents, Youth, Adults)

Parent Name (if applicable):__________________________________________
Participant Name:_________________________________________________
ID:_______________________________________________________________
Date of Scan:_______________________________________________________
Age at time of Scan:_______________________________________________
Date of Survey:_____________________________________________________

This survey and its questions pertain to the SDSU / UCSD fMRI study that you/ your child participated in on _____”date”______. We will be asking you about your/your child’s physical activity and exercise in the 6 months leading up to the day that she or he was scanned (or you were scanned) as part of our study. We ask that you try your best to answer all of the questions presented here, but if you do not know the answer to any question on this survey, please feel free to skip the question.

1. Who is the person completing this survey? (circle one answer only)
   A. Mother
   B. Other adult female
   C. Father
   D. Other adult male
   E. Adult participant
   F. Youth participant

2. Did you/your child have any medical conditions or disabilities that limited your/ his or her physical activity at the time of and six months leading up to the scan? (circle one answer only)
   A. No
   B. Yes, please specify:

3. What form of transportation did you/your child use to get to and from school? OR For adults, what form of transportation did you use to get to and from work?
(If the answer above question suggests physical activity, please ask the questions below)

   a. How many miles is it from your/the child’s home to the child’s school? OR How many miles is it from your home to your work place?
      a. 0-5
      b. 6-11
      c. 12-17
      d. 18-23
      e. 24 +
b. How many minutes per week did you/this child spend __________ (physical activity) to and from school/work?
   a. 1-30
   b. 31-60
   c. More than an hour
   d. More than two hours

c. Would you say that the majority of the path to and from school/work is
   a. down hill
   b. flat
   c. up-hill

The remainder of this survey is about you/your child's activities in the 6 months leading up to their fMRI scan that include activities performed at school, after school, at home, and on weekends. Please give all answers only about the child or teenager or adult who participated. Please take a moment to remember what major activities you/your child participated in around the time of the study. It may help you remember if you think about the following things:

What did you/this child do for recreation?
What sports, exercise, or physical activity teams, classes, lessons, or practices did you/this child participate in at that time?
Did you/this child go anywhere unusual for a weekend outing or after-school event in the 6 months leading up to the scan?
What activities did you/this child do with his or her friends?

We know that you may not know the precise amount of time your child spends in of all the activities you/this child does. You will have to make estimates of the amount of time you/this child spent in various activities. Once again, please think about your/your child’s activities in the 6 months leading up to the scan.

4. Was your child/Were you on a sports team at least 6 months prior to and leading up to the time of the scan?

If so, which sports was he / she (or were you) involved in?

How many times a week and for how long did you/your child actively engage in this sport?

5. In the 6 months leading up to the scan, what did you/your child usually do when he / she had a choice about how he / she spent recreational time? (circle one answer only)
   A. Almost always chose activities like TV, reading, listening to music, or computers
   B. Usually chose activities like TV, reading, listening to music, or computers
   C. Just as likely to choose active as inactive recreation
   D. Usually chose activities like bicycling, dancing, outdoor games, or sports
   E. Almost always chose activities like bicycling, dancing, outdoor games, or sports
6. How would you rate your/this child's level of physical activity in the 6 months leading up to the scan, compared to others of the same age and sex? (circle one answer only)
   A. Much less than others
   B. Somewhat less than others
   C. About the same
   D. Somewhat more than others
   E. Much more than others

7. How often did this you/child go to the nearest public park? (circle one answer only)
   A. None
   B. Rarely
   C. Sometimes
   D. Often
   E. Very often

8. If you/your child did go to the park, what form of transportation was used to get to and from the park?
   A. Physical activity
   B. Motorized transportation

9. On average, how many days a week did you/your child perform each activity and for how many hours per session was the activity performed?
   1. Aerobics/aerobic dancing
   2. Ball play: 4-square, dodge ball, kickball, catch
   3. Baseball/softball
   4. Basketball
   5. Bicycling or exercise cycling
   6. Calisthenics: push-ups, sit-ups, jumping jacks
   7. Cheerleading, marching band, drill team
   8. Climbing stairs for exercise, Stairmaster
   10. Dance classes (ballet, jazz, modem, tap, zumba)
   11. Football
   12. Field hockey
   13. Frisbee games
   14. Laborious chores (Gardening, yard work, mowing, mopping)
   15. Golfing
   16. Gymnastics, tumbling, trampoline
   17. Hiking
   18. Ice hockey
   19. Indoor or outdoor playground: swing, slide, monkey bars, kid sports
   20. Jumping rope
   21. Laser tag
   22. Martial arts: karate, judo
23. Outdoor play: war, climb trees, hide & seek
24. Racquet sports: tennis, squash, paddleball, badminton, etc.
25. Rowing or rowing machine
26. Running, jogging, treadmill
27. Skate boarding
28. Skating: ice, roller, in-line
29. Skiing: cross-country or NordicTrack
30. Skiing: downhill or water
31. Soccer
32. Swimming laps
33. Volleyball
34. Walking for exercise (including treadmill)
35. Walking for transportation
36. Water play: in pool or lake
37. Weight lifting
38. Wrestling
39. Surfing
40. Other

10. In general (across all activities), how many hours per week on average were you/was your child engaging in moderate to vigorous activity?

11. How confident are you in the accuracy of the estimates in the preceding list? (circle one answer only)
   A. Very confident
   B. Somewhat confident
   C. Not sure how confident
   D. Slightly confident
   E. Not at all confident

Lastly, what was your/your child’s height and weight at the time of the scan?

_________ Height (ft and inches)  ___________ Weight (lbs.)