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Research Report

Quantitative regional cerebral blood flow MRI of animal model of attention-deficit/hyperactivity disorder

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ABSTRACT

The spontaneously hypertensive rat (SHR) has been widely used as an animal model for attention-deficit/hyperactivity disorder (AD/HD), a developmental disorder that affects 3–5% of school-age children. Quantitative high-resolution ($180 \times 180 \times 1500 \mu\text{m}$) perfusion magnetic resonance imaging was performed to evaluate regional CBF in AD/HD rats (SHR, $n=7$) and control Wistar Kyoto rats (WKY, $n=9$) in the frontal cortex, motor cortex, sensory cortex, corpus callosum, hippocampus, thalamus, globus pallidus, caudoputamen and whole brain. The accuracy of repeated cerebral blood flow (CBF) measurements within animals in these brain regions ranged from 3% to 10% (7 repeated measures) and across animals ranged from 15% to 18% ($n=7$ rats), respectively, indicating highly accurate and reproducible CBF measurements. Regional CBF of the SHR were statistically different from those of the WKY rats in all structures analyzed ($P<0.05$) except for the caudate putamen ($P=0.09$) and the globus pallidus ($P=0.12$). Whole brain CBF of the SHR (1.5 ± 0.2 ml/g/min, mean \pm S.D.) was $\sim 25\%$ higher than that of the WKY rats (1.2 ± 0.2 ml/g/min), likely due to the hypertensive nature of the AD/HD rat model. Following normalization to eliminate global CBF differences, CBF in the medial prefrontal cortex, a structure thought to be the equivalent of the human dorsolateral prefrontal cortex and widely implicated in AD/HD, was found to be higher in SHR compared to WKY rats ($P<0.05$). The only other structure that was found to be statistically different after normalization is the corpus callosum ($P<0.05$). Since resting cerebral blood flow is intricately coupled to resting neural activity, these results suggest that there was abnormal resting neural activity in the medial prefrontal cortex and the corpus callosum between the control and AD/HD animals, consistent with the hyperactivity, impulsivity, inattention, and other AD/HD-like behaviors in this animal model.

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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is an early-onset developmental disorder that affects approximately 3–5% of school-age children and mainly occurs in males. It is marked by symptoms of inattention, hyperactivity, and im-

pulsivity, and is among the most prevalent of childhood disorders (American Psychiatric Association, 1994). In addition to the interpersonal and scholastic problems that accompany the disorder, children with ADHD also suffer from low self-images (Dumas and Pelletier, 1999) and are predisposed to develop other psychiatric problems later in life (Tarter et al.,

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2003). Furthermore, ADHD children show less persistence at academic tasks (Hoza et al., 2001). ADHD has also been shown to interact with comorbid learning disabilities to exacerbate handicaps in executive function (Seidman et al., 2001). Barkley describes ADHD as a failure in the brain circuitry responsible for behavioral inhibition and self-control. The dorsolateral prefrontal cortex is a key structure that is implicated in ADHD and is hypothesized to contribute to a combination of executive functions, including but not limited to working memory and internalization (Barkley, 1998).

With the advent of imaging technology, structural, functional and neurochemical profiles of many neurological and psychiatric disorders can be visualized across the entire brain at high spatial and temporal resolution. A plethora of structures have been identified to be associated with ADHD. Some of these prominent structures are the frontal lobes, basal ganglia, cerebellum, and frontal–basal ganglia circuitry (Amen, 1997; Casey et al., 1997; Giedd et al., 2001; Kates et al., 2002). Prefrontal volume has been found to be 8.3% smaller in ADHD boys (Mostofsky et al., 2002). Decreased prefrontal activation was observed in ADHD adolescents and was correlated with poorer performance on executive tasks (Rubia et al., 1999). A lower cerebral blood flow in the prefrontal cortices and the cerebellum in humans with ADHD has been reported using single photon emission computerized tomography (SPECT) (Kim et al., 2002). The resting CBF abnormalities were lateralized with a larger reduction in the right compared to the left prefrontal cortex (Spalletta et al., 2001).

Although experiments are often done on human subjects, animal models offer the means to study the mechanisms of the disease under well controlled conditions as well as increase the range of methods with which the disorder can be studied. The most widely used animal model for ADHD is the spontaneously hypertensive rat (SHR) because it shows many of the salient symptoms of ADHD, including hyperactivity and motor and cognitive impulsiveness (Sagvolden, 2000). SHR are bred from parental Wistar Kyoto rats (WKY) (Okamoto and Aoki, 1963) which do not show the quasi-ADHD symptoms, making the WKY strain an ideal control. Furthermore, a genetic model like the SHR, as opposed to an environmental model like abused or chemically treated rats (Sagvolden, 2000), should better represent a disease which has been shown to have a genetic component (Morrison and Stewart, 1971).

While cerebral blood flow (CBF) can be measured using autoradiography, positron emission tomography, SPECT, laser Doppler techniques, and many other techniques, CBF measurement using magnetic resonance imaging has some unique advantages. It is non-invasive, quantitative, high spatial resolution with whole brain coverage. CBF MRI can be measured by using an exogenous intravascular contrast agent or by magnetically labeling the endogenous water in blood (Calamante et al., 1999; Barbier et al., 2001). The former is efficient but it has lower spatial resolution because the long half life of the contrast agent allows only one CBF measurement per bolus injection, precluding the possibility of signal averaging needed for high spatial resolution measurements. Arterial spin labeling (ASL) techniques, on the other hand, are totally non-invasive, and the labeled water has a short half-

life (~blood T_1) making it possible to performed multiple repeated measurements which can be used to augment spatial resolution and/or signal-to-noise ratio.

ASL can be performed using pulsed labeling (Detre et al., 1994; Wong et al., 1998; Wang et al., 2005) or continuous labeling (Silva et al., 1997a; Zaharchuk et al., 1999; Talagala et al., 2004; Zhang et al., 1995); both are capable of multislice and whole-brain imaging. Continuous ASL (cASL) can be achieved with the same radiofrequency (RF) coil used for imaging or a separate neck coil. cASL with a separate neck coil is generally more sensitive relative to the single-coil technique (Kim, 1995; Wong et al., 1998; Wang et al., 2005), particularly in small animals such as rodents which have short arterial transit time. With the separate neck coil, magnetization-transfer effect is eliminated if the coils are properly decoupled, resulting in a larger signal difference between labeled and non-labeled images, and thus improved CBF SNR. RF power deposition is localized to the neck area and unlabeled images can be acquired without labeling RF, reducing specific absorption rate which could cause tissue heating. By quantifying the labeling efficiency, quantitative CBF in unit of ml per gram per min can be determined.

The goal of this study was to investigate the quantitative regional blood flow differences between the ADHD (SHR) and normal (WKY) rats under resting conditions. Since cerebral blood flow is intricately coupled to neural activity (Roy and Sherrington, 1890), we hypothesized that CBF measurements could offer insights into the regional neural activity differences between control and ADHD animals under resting conditions. Multislice high-resolution ($180 \times 180 \times 1500 \mu\text{m}$) quantitative perfusion imaging was performed using magnetic resonance imaging. The continuous arterial spin labeling technique using a two-coil system and echo-planar data acquisition was used. Quantitative cerebral blood flow (CBF) maps were derived. The accuracy of repeated CBF measurements within and across different animals was carefully evaluated. CBF differences between ADHD and control rats were analyzed for the medial prefrontal cortex, caudate nucleus, globus pallidus, frontal cortex, sensory cortex, motor cortex, thalamus, hippocampus, and whole brain.

2. Results

2.1. CBF reproducibility

Representative anatomic images from a WKY rat are shown in Fig. 1A. Representative regions of interest (ROIs) are shown overlaying the anatomic images which include the frontal cortex, the sensory cortex, the hippocampus, the thalamus, the globus pallidus, the caudate putamen, the corpus callosum, the medial prefrontal cortex, and the motor cortex. Representative high-resolution echo planar images (EPI) and quantitative CBF images from the same animal are shown in Figs. 1B and C, respectively. Heterogeneous CBF distribution across the entire brain was observed as expected (i.e., the corpus callosum and the lateral ventricles had lower CBF values).

We carefully evaluated the accuracy and consistency of CBF measurement within the same animal. Representative averages and standard deviations for seven sets of repetitions

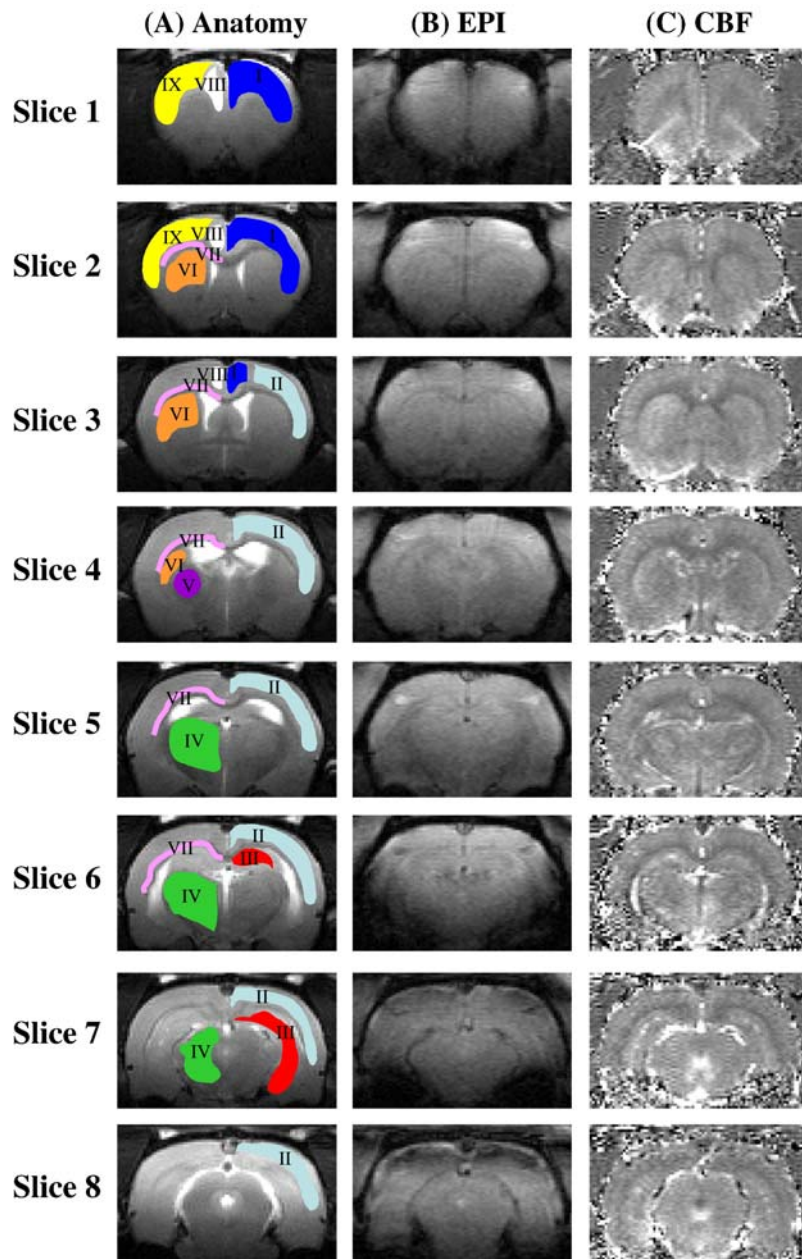


Fig. 1 – Anatomical images of a WKY rat. Overlaid on the anatomy are nine representative regions of interest (ROIs): I. Frontal cortex—dark blue; II. sensory cortex—light blue; III. hippocampus—red; IV. thalamus—green; V. globus pallidus—purple; VI. caudoputamen—orange; VII. corpus callosum—pink VIII. medial prefrontal cortex—white; IX. motor frontal cortex—yellow. ROI for each type of structure was drawn on one hemisphere for clarity; analysis used ROI's from both hemispheres. (B) Representative echo planar image (EPI) of a WKY rat. (C) Representative perfusion image from the same animal.

of the same WKY rat on the same day are shown in Table 1. The average whole-brain cerebral blood flow was 0.99 ± 0.04 ml/g/min (mean \pm S.D., 7 repetitions), and the standard deviations for the different brain sub-structures ranged from 0.03 to 0.10 ml/g/min. Since each rat was measured twice, the average percent differences for each ROI across the two repetitions of the same animal were also evaluated. The average percent differences ranged from 17% in the corpus callosum to 33% in the left medial frontal lobe with a whole brain average of 18%.

2.2. Resting cerebral blood flow differences between SHR and WKY rats

The group-average quantitative cerebral blood flow differences between WKY and SHR are shown in Fig. 2A. For WKY control rats, the CBF in different brain regions varied from 0.5 to 1.6 ml/g/min, indicating the heterogeneity of CBF distribution in the rat brain, with a whole brain average of 1.2 ± 0.2 ml/g/min. These quantitative CBF values are consistent with those reported previously under similar conditions

Table 1 – Representative averages and standard deviations for seven consecutive repetitions from one animal

Region of interest (ROI)	Average	S.D.
Whole brain	0.99	0.04
Frontal cortex	0.91	0.07
Sensory cortex	0.90	0.06
Hippocampus	0.98	0.05
Thalamus	1.09	0.03
Globus pallidus	0.58	0.04
Caudate putamen	1.00	0.06
Corpus callosum	0.52	0.05
Medial prefrontal cortex	1.02	0.09
Motor cortex	0.89	0.05
Right medial prefrontal cortex	1.02	0.08
Left medial prefrontal cortex	1.03	0.10

(Duong et al., 2000, 2001a; Sicard et al., 2003). For the SHR, CBF ranged from 0.7 to 2.4 ml/g/min with a whole brain average of 1.5 ± 0.2 ml/g/min. Sub-structures of the left and right hemispheres were analyzed separately but no statistical differences were found, and data of the left and right hemispheres were grouped together for statistical comparison between SHR and WKY rats. The global and regional quantitative CBF of the SHR and WKY rats were statistically different for all substructures analyzed ($P < 0.05$) except for at the caudate putamen ($P = 0.09$) and globus pallidus ($P = 0.12$). The differences between the two rat strains could be due in part to the SHR being hypertensive, which results in systemically higher resting blood flow across the entire brain.

Therefore, to further investigate the relative regional CBF differences between SHR and WKY rats, normalized CBF values with respect to the whole-brain average were analyzed (Fig. 2B). CBF in the medial prefrontal cortex and the corpus callosum of the SHR was found to be higher than the WKY rats ($P < 0.05$). No statistical differences in the normalized CBF values between SHR and WKY rats were observed in other brain structures analyzed ($P > 0.05$).

3. Discussion

This study reports regional CBF differences between SHR (AD/HD model) and WKY (controls) rats. Regional quantitative CBF of the SHR were statistically different from those of the WKY rats in all structures analyzed except for the caudate putamen and the globus pallidus. Following normalization to eliminate global CBF differences, CBF in the medial prefrontal cortex, a structure thought to be the equivalent of the human dorsolateral prefrontal cortex and widely implicated in AD/HD, was found to be higher in SHR compared to WKY rats. Since resting CBF is intricately coupled to resting neural activity, these results suggest that there was abnormal resting neural activity in the medial prefrontal cortex and the corpus callosum between the control and AD/HD animals, consistent with the hyperactivity, impulsivity, inattention, and other AD/HD-like behaviors in this animal model. These findings were made possible by high-resolution CBF measurements using the continuous arterial spin labeling technique.

3.1. Consistency of cerebral blood flow measurements within and across animals

MRI offers a non-invasive tool to image quantitative CBF at reasonably high spatial and temporal resolution at the level of the capillary and tissue (Duong et al., 2001b; Kim, 1995; Kwong et al., 1992; Wong et al., 1998). While consistent with many existing and established invasive CBF measurements, the arterial spin labeling technique used to measure cerebral blood flow herein is subject to errors that could compromise the precision of CBF measurements. These errors could arise from magnetization transfer, transit time, and water-exchange effect. With the use of the actively decoupled two-coil system for CBF measurements, the magnetization transfer effect on quantitative CBF values was not an issue (Duong et al., 2000; Silva et al., 1999). Transit time (Calamante et al., 1999; Zhou and van Zijl, 1999) and water-exchange effects have been shown to be small (Parkes and Tofts, 2002; Silva et al., 1997a; Zhou et al., 2001) and are not expected to alter the overall conclusions of this study.

We carefully evaluated the accuracy of repeated measurements within and across animals. The differences in experimental setup, animal size, blood gases, animal physiology and temperature could potentially affect the accuracy of the CBF measurements. In this study, similar animal size and experimental setup were used. A previous study (Sicard et al., 2003) in which animal physiology, such as blood gases, blood pressure, respiration and heart rates were carefully evaluated under identical experimental conditions, showed that all animals had normal physiological parameters. Therefore, these physiological parameters were not measured in this study to avoid being invasive. For consistency within the same rats on the same day, we observed regional and whole-brain differences of $\sim 4\%$. Consistency across animals in the same group was $\sim 18\%$ for the WKY group and $\sim 15\%$ for the SHR group. These compared favorably with $\sim 25\%$ difference in alpha-chloralose anesthetized and mechanically ventilated animals (Duong et al., 2000).

3.2. Resting cerebral blood flow differences between SHR and WKY rats

This study aimed at evaluating the cerebral blood flow differences between the spontaneously hypertensive rat (SHR) and its non-ADHD Wistar Kyoto (WKY) kin. This was done in hopes of revealing the relevance of SHR as a model for attention-deficit/hyperactivity disorder (ADHD). We observed significant increase in resting blood flow in the SHR relative to the WKY rats for all sub-structures analyzed except for the caudate putamen and globus pallidus. The global increase in blood flow across the entire brain could be attributed in part to the hypertensive nature of this rat model which may have nothing to do with ADHD characteristics. We therefore normalized CBF with respect to the whole brain CBF value and this normalization should remove the hypertensive component of the animal model.

When the regional CBF values were normalized with respect to the whole brain average for each animal, the medial prefrontal cortex showed a consistent and significant higher blood flow in SHR compared to WKY rats. The medial

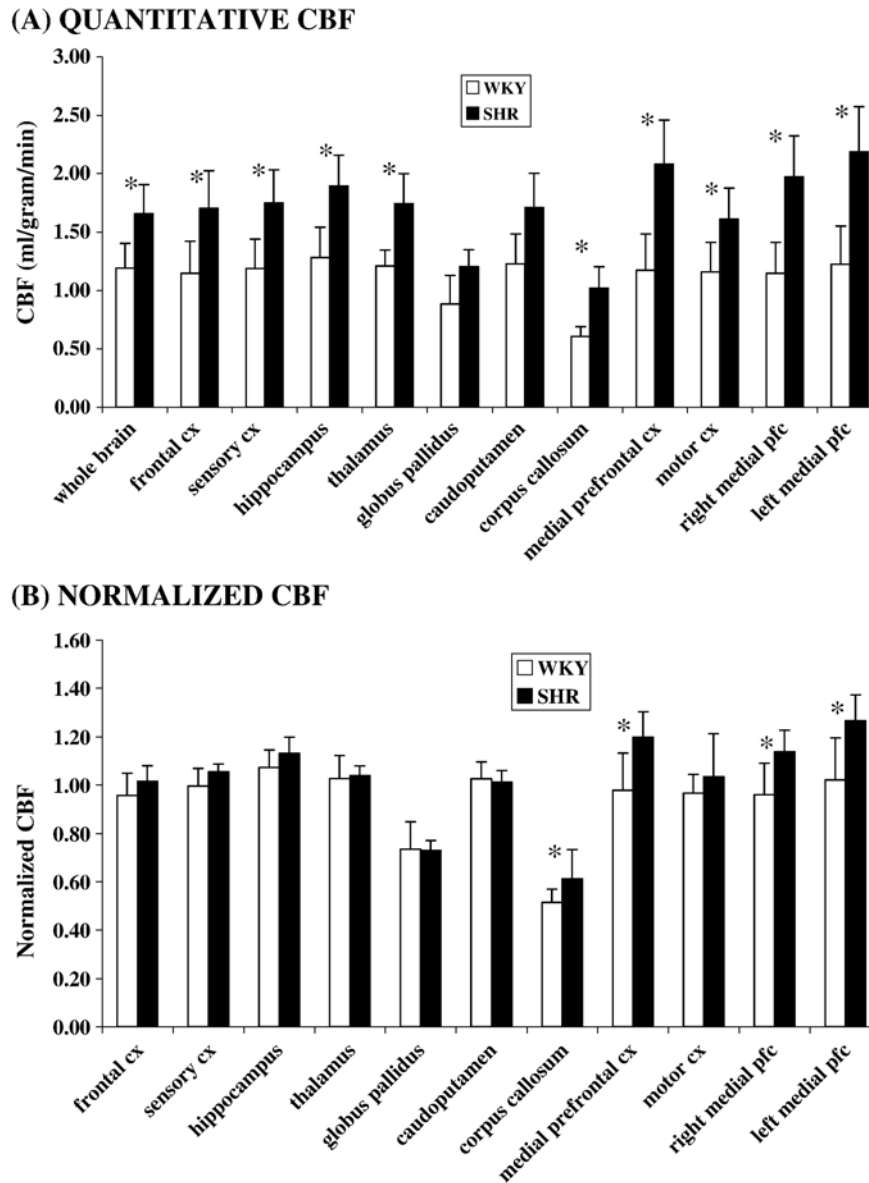


Fig. 2 – (A) Quantitative cerebral blood flow from different brain structures of SHR (black, $n=7$, mean \pm S.D.) and WKY rats (white, $n=9$) using the ROIs in Fig. 1. (B) Normalized cerebral blood flow from different regions of interests of SHR and WKY rats. Values were normalized by dividing the CBF values of individual structures by the whole brain average. * $P < 0.05$. CX: cortex, pfc: prefrontal cortex.

prefrontal cortex in rats is thought to be equivalent of the primate dorsolateral prefrontal cortex (Akert, 1964; Rose and Woolsey, 1948a,b, 1949), although it is still debated whether rats have such a homologous structure (Preuss, 1995). The dorsolateral prefrontal cortex is purported to play a central role in ADHD (Barkley, 1998; Giedd et al., 2001). There have been a few studies on anatomical, functional and perfusion differences centered around the prefrontal cortex and more specifically the dorsolateral prefrontal cortex. Smaller frontal lobes have been reported in ADHD boys relative to age-matched controls (Mostofsky et al., 2002). ADHD children showed smaller prefrontal activation involving motor responses and these findings were correlated with poorer behavioral performance (Rubia et al., 1999). Decreased resting

blood flow in the prefrontal cortex in ADHD children relative to controls had been reported as measured by SPECT (Kim et al., 2002). The resting CBF abnormalities have also been found to be lateralized with larger reduction in the right compared left prefrontal cortices (Spalletta et al., 2001).

In contrast to the human CBF studies, the resting CBF in the medial prefrontal cortex of ADHD rats was found to be consistently higher than that of the WKY control rats. Our data is consistent with the findings of increased norepinephrine activity in prefrontal cortex slices of the same SHR model relative to the WKY rats (Russell et al., 2000). Given the accuracy, consistency and reproducibility of our CBF measurements, the CBF differences in the medial prefrontal cortex of ADHD between SHR and WKY rats are very unlikely to be

artificial. Discrepancies between the human and animal CBF data could be due to the SHR rat model itself or due to the use of anesthetics. As with any animal models of human disorders or diseases, it is possible that the SHR do not perfectly model the ADHD conditions in humans. Furthermore, anesthetized animals were used in our study in contrast to the human studies, which generally use conscious patients. Anesthetics, widely used in magnetic resonance imaging of animal models to avoid movement artifacts, are known to affect resting blood flow and neural activity. In particular, isoflurane is a potent vasodilator (Hensen et al., 1988; Matta et al., 1999) which could partially mask regional differences between the experimental and control groups. Our lab has recently developed technology for quantitative CBF measurements in conscious rats (Sicard et al., 2003). CBF comparison of awake and anesthetized models of the SHR and WKY rats are under investigation, which could potentially yield additional insight into this ADHD rat model.

Similarly, after normalization, CBF values of the corpus callosum showed a significantly higher blood flow in SHR compared to WKY rats. This result needs to be interpreted with caution because of its small size and the potential for partial volume effect. A smaller rostral corpus callosum in ADHD children had been reported relative to controls (see review; Giedd et al., 2001). It has also been suggested that the cortical-striatal circuitry is impaired in ADHD patients (Amen, 1997; Casey et al., 1997; Giedd et al., 2001; Kates et al., 2002). Our resting CBF data in the corpus callosum is consistent with these findings. Other studies reported functional abnormality in the cerebellum in ADHD patients (Giedd et al., 2001). Cerebellum CBF was not measured in our study. Probe electronics are currently being developed for imaging cerebellar CBF.

One major implication of our findings is that caution must be exercised when comparing stimulus-evoked fMRI responses between normal and ADHD in rats and/or humans. We observed ~25% CBF differences (whole brain average) between ADHD and control rats. It has been shown that the resting blood flow level markedly modulates the magnitude and the dynamics of the stimulus evoked BOLD responses (i.e., time to peak and full-width at half maximum of the fMRI response function). Higher resting CBF yields a smaller stimulus-evoked fMRI BOLD percent change, and a slower, broader hemodynamic response associated with visual stimulation (Cohen et al., 2002; Kemna and Posse, 2001). Therefore, these results suggest that caution must be exercised when comparing stimulus-evoked fMRI responses between SHR and WKY animals.

In summary, we employed high-resolution CBF arterial spin-labeling technique to study normal and AD/HD rats. The accuracy of repeated CBF measurements using MRI on different brain substructures was reported to be 3–10% within the same animal and 15–18% across animals, suggesting highly accurate and reproducible quantitative CBF measurements. ADHD rats showed markedly higher regional and global blood flow when compared to the control WKY rats. After normalization to eliminate the global differences, regional CBF in the ADHD rats showed differentially higher CBF in the corpus callosum and the medial prefrontal cortex; the latter has been widely implicated in ADHD.

4. Experimental procedures

4.1. Animal preparation

All animal experiments were approved by IACUC and in accordance with guidelines published by the NIH. Two groups of male rats (356 ± 48 g), were imaged. *Group I* consisted of Wistar Kyoto rats (WKY, $n=9$, control). *Group II* consisted of spontaneously hypertensive rats (SHR, $n=7$, experimental). Typically, each rat was imaged twice on different days. Animals were secured in a MR-compatible rat stereotaxic headset with custom-designed ear- and tooth-bars with a built-in radiofrequency neck coil for arterial spin labeling. All imaging studies were performed under 2% isoflurane, in which animals respired spontaneously without mechanical ventilation. The rectal temperature was monitored and maintained at 37.5 ± 1 °C throughout the study via a feedback-regulated, circulating-water pad.

4.2. MR experiments

All MR experiments were performed on a 4.7-T/40-cm horizontal magnet (Oxford, UK) equipped with a Biospec Bruker console (Bruker, Germany), and a 20-G/cm magnetic field gradient insert (ID=12 cm) capable of 120- μ s rise time (Bruker, Germany). An actively-decoupled surface coil (2.3-cm ID) was used for brain imaging and a neck coil (Duong et al., 2000; Silva et al., 1999) for perfusion labeling. Coil-to-coil electromagnetic interaction was actively decoupled. High-resolution anatomical images were acquired using the fast spin-echo (rapid acquisition with relaxation enhancement, RARE) pulse sequence with TR=2 s (90° flip angle), 16 echo trains, effective TE=85 ms, matrix=256×256, FOV=2.56×2.56 cm², and eight 1.5-mm slices. Sixteen transients were acquired for signal averaging.

CBF measurements were made using the continuous arterial spin-labeling technique (Duong et al., 2000; Silva et al., 1999) with four-shot, gradient-echo, echo-planar-imaging (EPI) acquisition. Paired images were acquired alternately—one with arterial spin labeling and the other without spin labeling (control). The MR parameters were: data matrix=128×128, FOV=2.56×2.56 cm², the same eight 1.5-mm slices as anatomy, TE=15 ms, and TR=2 s per shot (90° flip angle). Continuous arterial spin labeling employed a 1.78-s square radiofrequency pulse to the labeling coil in the presence of 1.0 G/cm gradient along the flow direction such that the condition of adiabatic inversion was satisfied (Detre et al., 1992). The sign of the frequency offset was switched for control (non-labeled) images. The total time for one pair of images is 16 s. For each set of CBF measurement, 31 pairs of images (~8 min) were acquired and the first pair was discarded and excluded from analysis. This was repeated 6–8 times for each imaging session (~60 min), and the resulting values were averaged.

4.3. Data analysis

Image analysis employed codes that were written in Matlab (MathWorks Inc, Natick, MA) and the STIMULATE software (Strupp, 1996). CBF image (S_{CBF}) with intensity in unit of ml per

gram tissue per min was calculated pixel-by-pixel using (Silva et al., 1997b),

$$S_{\text{CBF}} = \frac{\lambda}{T_1} \frac{S_C - S_L}{S_L + (2\alpha - 1)S_C} \quad (1)$$

where S_C and S_L are signal intensities of the control and labeled images, respectively. λ is the water brain–blood partition coefficient, T_1 is that of tissue, and α is the arterial spin-labeling efficiency (Silva et al., 1997b). λ was taken to be 0.9 (Herscovitch and Raichle, 1985). T_1 and α were measured to be 1.5 s and 0.75, respectively.

Multiple CBF measurements from each animal were averaged to obtain a single multi-slice set of CBF images. Regions of interests (ROIs) were analyzed in both hemispheres and were carefully drawn with reference to both anatomy and CBF images. These ROIs were the whole brain, frontal cortex, medial prefrontal cortex, motor cortex, sensory cortex, corpus callosum, hippocampus, thalamus, globus pallidus, and caudoputamen. Accuracy and consistency of repeated CBF measurement within and across different animals were evaluated. Differences in resting CBF values in different brain structures between SHR and WKY rats were compared. In addition, relative differences in regional CBF with respect to the whole brain average were also analyzed by dividing the regional CBF values by the average CBF values of the whole brain for each animal. Statistical tests between SHR and WKY rats were performed by using the unpaired Student's *t*-test assuming unequal variances. All reported values and error bars on plots were in mean \pm S.D.

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