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Magnetic resonance imaging of cerebrovascular reactivity in healthy adolescents

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ABSTRACT

Background: Cerebrovascular reactivity (CVR), an important measure of cerebrovascular health in adults, has not been examined in healthy adolescents. Beyond the direct importance of understanding CVR in healthy youth, studies on this topic can yield insights regarding brain disease. We set out to evaluate 3 different CVR modelling approaches.

New Method: Thirty-nine healthy adolescents (ages 13–19 years, 20 females) completed six blocks of 15-second breath-holds separated by 30-second blocks of free-breathing. CVR was measured using blood-oxygenation-level dependent functional magnetic resonance imaging at 3-Tesla; voxel-wise analyses were complemented by regional analyses in five major subdivisions of the brain. Hemodynamic response functions were modelled using: (1) an individualized delay term (double-gamma variate convolved with a boxcar function), (2) with a standard 9-second delay term, and (3) a sine-cosine regressor.

Results: Individual-delay yielded superior model fit or larger cluster volumes. Regional analysis found differences in CVR and time-to-peak CVR. Males had higher brain-wide CVR in comparison to females ($p = 0.025$, $\eta^2_{part} = 0.345$). BMI and blood pressure were not significantly associated with CVR (all $p > 0.4$).

Comparison with Existing Methods: This was the first study to compare these methods in youth. Regional differences were similar to adult studies.

Conclusions: These findings lend support to future breath-hold CVR studies in youth, and highlight the merit of applying individualized-delay estimates. Regional variability and sex-related differences in CVR suggest that these variables should be considered in future studies, particularly those that examine disease states with predilection for specific brain regions or those diseases characterized by sex differences.

1. Introduction

Cerebrovascular reactivity (CVR) is the capacity of the brain's blood vessels to dilate or constrict in response to vasoactive substances (Yezhuvath et al., 2009). Studies of CVR in healthy adults have been instrumental in establishing normative data that can be used to understand aberrant cerebrovascular function in disease (Bright et al., 2009; Kastrup et al., 1999a, 2001). CVR induction methods include using the carbonic anhydrase inhibitor, acetazolamide (Inoue et al., 2014), and hypercapnia (i.e. high levels of carbon dioxide [CO_2] in the blood) (Bright et al., 2009). Of these methods, hypercapnia, triggered via CO_2 inhalation has become a standard, however, it still raises concerns over invasive procedures (Urback et al., 2017) and possible side-effects of panic and anxiety symptoms in a subset of individuals (Sanderson and Wetzler, 1990; Van den Hout and Griez, 1984). As a result, hypercapnia research in adolescents, while producing some limited findings of interest in acute patient populations (Han et al., 2011; Ostrovskaya et al., 2015; Wong et al., 2011), remains understudied (Urback et al., 2017). In the present study, we focused on this gap in the literature using a non-invasive breath hold (BH) CVR task

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during functional magnetic resonance imaging (fMRI) in healthy adolescents and compared three potential methods for analyzing this data.

CVR can be quantified both in terms of the spatial extent of voxels that reach the predetermined threshold and the amplitude of response: a greater spatial extent and larger amplitude are considered markers of better cerebrovascular health (Bright and Murphy, 2013; Glodzik et al., 2013). A second important metric of vascular health available via the BH paradigm is time-to-peak CVR (TTP): the time difference between the end of the BH and the peak blood-oxygenation-level dependent (BOLD) signal. Studies have shown longer delays in individuals with intracranial stenosis and severe carotid stenosis (Donahue et al., 2015; Hetzel et al., 2003) and high altitude participants compared to sea level participants (Yan et al., 2011). Longer TTP times are consistent with lower CVR and poorer cardiovascular health (Donahue et al., 2015; Hetzel et al., 2003; Yan et al., 2011).

Youth (i.e. child or adolescent) studies of CVR in patient populations are less common, compared to similar adult studies (Buterbaugh et al., 2015; Haight et al., 2015; Tchistiakova et al., 2014). Among youth, there is evidence of low CVR among individuals with hypertension (Ostrovskaya et al., 2015; Pall et al., 2011; Settakis et al., 2003, 2006; Wong et al., 2011), type 1 diabetes (Lin et al., 2015; Rosengarten et al., 2002), severe head injuries (Sharples et al., 1995), and cerebral vasculopathy (Han et al., 2011) and elevated CVR in youth with migraine headaches (Rosengarten et al., 2003) and chronic renal failure (Szprynger et al., 2000). The majority of these studies use transcranial Doppler ultrasound (TCD). No TCD study has examined regional CVR differences in healthy adolescents.

TCD measures CVR based on blood flow velocity in major cerebral arteries (i.e. middle cerebral artery), and is suboptimal for characterizing microvascular reactivity (Lythgoe et al., 1999). This limits signal detection of early subclinical signs of cerebrovascular disease arising first in microvasculature, (Pugh and Lipsitz, 2002; Riddle et al., 2003) and misses potential opportunities of early intervention. FMRI has emerged as a popular choice for measuring CVR because, in contrast to other methods such as TCD (Persoon et al., 2012; Rijbroek et al., 2009; Ringelstein et al., 1988), positron emission tomography, and single-photon emission computed tomography (Ogasawara et al., 2003), fMRI is non-invasive, and provides good spatial and temporal resolution for whole-brain imaging. To our knowledge, a single study investigated whole-brain CVR in a healthy youth sample using MRI (Thomason et al., 2005). That study compared BH-CVR between 16 healthy children and 16 healthy young adults, finding that signal-to-noise ratio was greater in adults. Additionally, spatial extent was greater in adults and TTP was shorter in children. This study did not examine regional differences or associations with vascular risk factors such as BMI and blood pressure.

One fMRI study in healthy adults has drawn attention to the importance of regional differences in CVR (Kastrup et al., 1999a) (cerebellum > visual cortex > sensorimotor cortex > frontal > basal ganglia) and TTP (occipital > frontal and parietal) (Blockley et al., 2011). In terms of demographic characteristics, CVR among adults is negatively associated with age (Kannurpatti et al., 2010; Lu et al., 2011; Riecker et al., 2003) and is increased in males vs. females (Kassner et al., 2010).

There are various model-based approaches to analyze BH-CVR. Adult studies have reported use of sine-cosine wave at the task frequency (Lipp et al., 2015; Murphy et al., 2011), or the more widely used hemodynamic response function convolved with a box-car function (Murphy et al., 2011; Tchistiakova et al., 2014) for modeling the CVR data. The latter method often incorporates a shift in the model based on a standard delay for all participants (Haight et al., 2015; Murphy et al., 2011), however a select few studies have used an individualized delay (Bright et al., 2009, 2011; Haight et al., 2015; Tchistiakova et al., 2014).

The BH paradigm yields a unique fMRI response. As opposed to most fMRI tasks (e.g. finger-tapping) BOLD signal increases after a relatively longer delay (Raut et al., 2016), and increases gradually throughout the whole duration of the BH (Murphy et al., 2011). This is the reasoning for the use of a sine-cosine model, adjusting for the progressive increase in the BOLD signal, peaking at the end of the BH. The individualized delay (based on each participant's unique hemodynamic response curve) and standard-delay (e.g. 9 s) models compensate for the longer BOLD signal delay of the vascular response to the BH.

Numerous methodological studies have refined the BH-CVR method. For instance, studies have compared the utility of end-expiration versus end-inspiration BH designs (Urback et al., 2017). End-inspiration BH-CVR has more confounds compared to end-expiration, such as inspiration depths (Birn et al., 2006) and delayed TPP (Kastrup et al., 1999b). A recent BH-CVR systematic review found the end-expiration BH method to be advantageous over the end-inspiration technique due to shorter TTP, less confounding variables, and no biphasic response (Urback et al., 2017). Methodological BH-CVR studies have also investigated BH length. Studies have shown significant BH-CVR signal changes after brief BHs, i.e. 6–10 seconds (Abbott et al., 2005; Liu et al., 2002), and diminishing increases in the BOLD signal for BHs greater than 20 s (Liu et al., 2002).

This study has three main objectives to better understand CVR in healthy adolescents. First, we compare the utility of sine-cosine and phase delayed boxcar modeling of the BH-CVR response. Examining this topic in adolescents specifically is important, as the rapid drop in CBF that occurs during adolescence (Biagi et al., 2007) may affect CVR modeling methods unique to this age group. Second, we investigate regional distribution of CVR. Finally, we explore the role of demographic characteristics in relation to CVR. We further sought to examine the association of CVR with BMI and blood pressure within the general normal range of the sample. Based on prior findings in adults and youth, we hypothesize that greater CVR would be associated with male sex, and lower BMI and blood pressure. Although age is not an outcome of central interest in this cross-sectional study with a youth sample, we include age as a covariate.

2. Materials and methods

2.1. Participants

The study protocol was approved by the Research Ethics Board at the Sunnybrook Health Science Centre. Written informed consent by the participant and one parent/guardian was obtained prior to study procedures. Participants were recruited from the community via advertisements, and included 48 healthy English-speaking adolescents (22 males, 26 females) aged 13–19 years (inclusive). Exclusion criteria were as follows: any major lifetime psychiatric disorder or any substance use disorder or anxiety disorder in the past 3 months, existing cardiac condition, auto-immune illness, inflammatory illness, taking anti-inflammatory, anti-platelet, anti-lipidemic, anti-hypertensive, hypoglycemic agent, infectious illness within the last 14 days, contraindications to MRI, health condition or physiological impairment that would preclude participation from exercise, neurological or cognitive impairment, and unable to provide informed consent. Participants arrived in the morning after fasting at least 8 h, were provided breakfast, and did not exercise prior to CVR measurement as the current study was part of a larger project that included aerobic exercise immediately following the assessment of CVR. After excluding participants for non-compliance during the BH task (n = 4), excessive head motion (mean rotational displacement > 0.46, n = 4), and artifacts in the fMRI image (n = 1), 39 participants (19 males, 20 females) remained.

2.2. Clinical and demographic information

Height and weight were measured by a stadiometer and SECA scale, respectively, using accepted standards (Krebs et al., 2007). Weight was adjusted for clothing using the following adjustments: subtract 1.4 kg