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Age dependence of hemodynamic response characteristics in human functional magnetic resonance imaging

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ABSTRACT

Functional magnetic resonance imaging (fMRI) studies of cognitive aging have generally compared the amplitude and extent of blood oxygen level-dependent (BOLD) signal increases evoked by a task in older and younger groups. BOLD is thus used as a direct index of neuronal activation and it is assumed that the relationship between neuronal activity and the hemodynamic response is unchanged across the lifespan. However, even in healthy aging, differences in vascular and metabolic function have been observed that could affect the coupling between neuronal activity and the BOLD signal. Here we use a calibrated fMRI method to explore vascular and metabolic changes that might bias such BOLD comparisons. Though BOLD signal changes evoked by a cognitive task were found to be similar between a group of younger and older adults (e.g., 0.50 ± 0.04% vs. 0.50 ± 0.05% in right frontal areas), comparison of BOLD and arterial spin labelling (ASL) responses elicited in the same set of structures by a controlled global hypercapnic manipulation revealed significant differences between the 2 groups. Older adults were found to have lower responses in BOLD and flow responses to hypercapnia (e.g., 1.48 ± 0.07% vs. 1.01 ± 0.06% over gray matter for BOLD and 24.92 ± 1.37% vs. 20.67 ± 2.58% for blood flow), and a generally lower maximal BOLD response *M* (5.76 ± 0.2% vs. 5.00 ± 0.3%). This suggests that a given BOLD response in the elderly might represent a larger change in neuronal activity than the same BOLD response in a younger cohort. The results of this study highlight the importance of ancillary measures such as ASL for the correct interpretation of BOLD responses when fMRI responses are compared across populations who might exhibit differences in vascular physiology.

1. Introduction

Aging is associated with a variety of changes in the brain. Though atrophy and white matter lesions are observable at the later stages in life (Brown et al., 2011; Salat et al., 2004), functional changes can also be observed (Chen et al., 2011; Lu et al., 2011). The effect of aging on the blood oxygen level-dependent (BOLD) signal evoked by a variety of tasks has been the subject of intense research in recent years and typical patterns of change are starting to emerge. Though several theories have been put forward to categorize and explain these patterns (Cabeza, 2002; Davis et al., 2008; Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Cappell, 2008; Reuter-Lorenz and Park 2010; Schneider-Garces et al., 2010), the complexity of the age-related changes observed indicate that there might be several mechanisms at play (Cabeza et al., 2005; Reuter-Lorenz and Park 2010). One of the most frequently observed pattern of change is a decreased lateralization of frontal BOLD responses, often detected as a decreased left frontal activation but an increased right frontal BOLD signal increase in older participants (Cabeza, 2002; Reuter-Lorenz and Park 2010). These differences in BOLD signal patterns have typically been explained by some form of compensatory neuronal activity in older participants to counterbalance the effects of loss of function and decreased primary perception or processing capacity (Cabeza, 2002; Cabeza et al., 2005; Davis et al., 2008; Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Cappell, 2008; Reuter-Lorenz and Park 2010). Implied in this type of theory is the fact that the additional recruitment should provide an advantage in terms of reduced age-related effects, usually observed as lower error rates or faster reaction times.

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However, most of the results used to devise these theories are based on hemodynamic imaging techniques, with BOLD contrast at the forefront. Therefore, one of the main sources of potential confounds in functional magnetic resonance imaging (fMRI) studies of aging stems from the ambiguous nature of the BOLD signal, which makes it difficult to draw physiologically specific conclusions from the amplitude and spatial extent of observed changes. The increases in BOLD signal observed during tasks arise from concomitant local changes in blood flow, blood volume, and oxidative metabolism. This complicates the direct, quantitative comparison of BOLD signal changes between groups, especially when changes in hemodynamic function across groups are suspected (Ances et al., 2009; Chen et al., 2011; Lu et al., 2011; Mohtasib et al., 2012; Samanez-Larkin and D'Esposito, 2008). Because BOLD can only be expressed as a fractional change from an unknown baseline, differences in the extent or amplitude of the BOLD signal might simply reflect an altered baseline state rather than a change in neuronal activity. For example, a similar metabolic change or vascular response from a lower metabolic or cerebral blood flow (CBF) baseline could artificially inflate the BOLD response.

Changes in BOLD signal might also reflect a decreased vascular reactivity (Lu et al., 2011). Aging is known to be associated with hardening of blood vessels throughout the body (Brown and Thore, 2011; O'Rourke and Hashimoto, 2007). Increased rigidity in vessels of the brain could lead to a decreased vascular response to a given metabolic demand. This would then result in a lower BOLD signal change in older individuals with neuronal activity levels similar to those seen in younger individuals. All these potential sources of confounds make the interpretation of BOLD signal comparisons between groups more difficult. However, some of these difficulties in interpretation could be alleviated by obtaining more physiologically-specific signals. The framework of calibrated fMRI, in which ASL and controlled vascular manipulations are added to BOLD, might be ideal for this because the end result and intermediate steps can be informative in determining the sources of age-related changes in hemodynamic properties (Gauthier et al., 2012).

Calibrated fMRI techniques allow quantitative comparisons between groups by isolating the oxidative metabolic component of the BOLD response to a task, which can be expressed as the percent change in cerebral metabolic rate of O_2 consumption ($CMRO_2$) (Blockley et al., 2012; Chiarelli et al., 2007; Davis et al., 1998; Gauthier and Hoge, 2012a). The most widely adopted techniques have used respiratory manipulations to determine the change in BOLD signal produced by a controlled vascular challenge. The gas manipulations used have included hypercapnia (Davis et al., 1998; Hoge et al., 1999a) (breathing increased concentrations of CO_2), hyperoxia (Chiarelli et al., 2007) (breathing increased concentrations of O_2), or a combination of both (Gauthier and Hoge, 2012a; Gauthier et al., 2011). Hyperoxia increases the O_2 content of blood, and hypercapnia leads to large and well characterized changes in blood flow throughout gray matter from the vasodilatory properties of CO_2. Both these manipulations give rise to substantial increases in BOLD signal throughout the brain that can, in combination with quantification of the concomitant CBF change evoked, be used to characterize the vascular component of the BOLD signal (Goode et al., 2009; Hoge et al., 1999b; Ito et al., 2008; Mark et al., 2010; Stefanovic et al., 2006; Tancredi et al., 2012). More specifically, calibrated fMRI experiments use the CBF and BOLD response to a gas manipulation to estimate the maximum possible BOLD signal change, M. This calibration factor M corresponds to the BOLD signal that would be obtained from complete elimination of deoxygenated hemoglobin from cerebral veins. When this vascular component is estimated, it can be factored out of the BOLD response evoked by an experimental task, to yield an estimate of the $CMRO_2$ component of the task-evoked BOLD signal change measured. We have recently described an extension of previous models (Chiarelli et al., 2007; Davis et al., 1998) that takes into account arbitrary changes in both blood flow and oxygen content (Gauthier and Hoge, 2012a). This model will be used here to more accurately take into account blood flow and oxygenation changes caused by breathing manipulation.

In the present study, we have used hypercapnically calibrated fMRI to investigate the effects of aging on the different components of the hemodynamic response, in the context of a cognitive task that has often been used to assess age-related cognitive deficits. Several studies have reported a larger Stroop effect (increases in reaction time and error rates to conflicting textual cues) and task switching cost in older compared with younger adults (DiGirolamo et al., 2001; Jimura and Braver, 2010; Langenecker et al., 2004; Milham et al., 2002; Mohtasib et al., 2012; Prakash et al., 2011; Wasylyshyn et al., 2011; Yun et al., 2011; Zysset et al., 2007). A modified Stroop task previously used by our group (Gauthier et al., 2012) and involving an element of interference and of switching is used here to identify the brain regions in which age-related effects might be expected. This study therefore investigates the effects of two functional challenges: the modified Stroop task, which is typical of cognitive tasks that might be explored in a BOLD aging study, and a hypercapnic respiratory manipulation. The combination of acquisitions during these two functional challenges is used to investigate possible biases and confounds associated with BOLD studies of cognitive aging. Calibrated fMRI is used to estimate a number of vascular and metabolic parameters that jointly determine the final BOLD signal compared between young and old in typical fMRI studies of aging. These parameters might be used to assess the validity of direct BOLD signal comparisons between age groups. Because baseline blood flow and vascular reactivity are both expected to decrease with age (Chen et al., 2011; Lu et al., 2011), it might be that the maximal BOLD signal change is lower in older individuals, leading to bias in the interpretation of age-related BOLD signal differences.

2. Methods

2.1. Participants

Acquisitions were conducted in 31 young (10 female, with mean age of 24 ± 3 years) and 31 older (14 female, with mean age of 64 ± 5 years) healthy participants on a Siemens TIM Trio 3T magnetic resonance imaging (MRI) system (Siemens Medical Solutions, Erlangen, Germany) using the vendor-supplied 32-channel receive-only head coil for all acquisitions. All subjects gave informed consent and the project was approved by the local ethics committee (Comité mixte d'éthique de la recherche du Regroupement Neuroimagerie/Québec).

Exclusion criteria for this study included claustrophobia, cardiac disease, hypertension or taking blood pressure lowering medication, neurological or psychiatric illness, smoking, excessive drinking (more than 2 drinks per day), thyroid disease, diabetes, asthma, and using a regular treatment known to be vasoactive or psychoactive. Participants were all nonsmokers and older participants had all been nonsmokers for at least 5 years. Additionally, every participant had a fasting blood draw on the morning of the magnetic resonance acquisition day to ensure that their fasting blood glucose and cholesterol levels were normal, and older participants met with a geriatric MD to ensure that they did not meet any of the exclusion criteria for the study.

All participants completed a short neuropsychological screening battery to assess verbal reasoning (Similarities subtest of the Wechsler Adult Intelligence Scale III; WAIS-III) (Wechsler, 1997), short-term memory (Digit span forward of WAIS-III), working