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Hypercapnic evaluation of vascular reactivity in healthy aging and acute stroke via functional MRI

Ryan V. Raut[a,*], Veena A. Nair[a], Justin A. Sattin[b], Vivek Prabhakaran[a,b]

[a]Department of Radiology, University of Wisconsin-Madison, Madison, WI 53792, USA
[b]Department of Neurology, University of Wisconsin-Madison, Madison, WI 53792, USA

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ABSTRACT

Functional MRI (fMRI) is well-established for the study of brain function in healthy populations, although its clinical application has proven more challenging. Specifically, cerebrovascular reactivity (CVR), which allows the assessment of the vascular response that serves as the basis for fMRI, has been shown to be reduced in healthy aging as well as in a range of diseases, including chronic stroke. However, the timing of when this occurs relative to the stroke event is unclear. We used a breath-hold fMRI task to evaluate CVR across gray matter in a group of acute stroke patients (<10 days from stroke; $N = 22$) to address this question. These estimates were compared with those from both age-matched ($N = 22$) and younger ($N = 22$) healthy controls. As expected, young controls had the greatest mean CVR, as indicated by magnitude and extent of fMRI activation; however, stroke patients did not differ from age-matched controls. Moreover, the ipsilesional and contralesional hemispheres of stroke patients did not differ with respect to any of these measures. These findings suggest that fMRI remains a valid tool within the first few days of a stroke, particularly for group fMRI studies in which findings are compared with healthy subjects of similar age. However, given the relatively high variability in CVR observed in our stroke sample, caution is warranted when interpreting fMRI data from individual patients or a small cohort. We conclude that a breath-hold task can be a useful addition to functional imaging protocols for stroke patients.

1. Introduction

Functional magnetic resonance imaging (fMRI) has made important contributions to our understanding of post-stroke brain changes. fMRI can provide valuable insight in terms of characterizing brain plasticity changes as well as the prediction of outcomes and assessment of recovery after stroke (Calautti and Baron, 2003; Heiss and Kidwell, 2014; Ward et al., 2003). However, there is growing concern over the integrity of the blood oxygenation level-dependent (BOLD) signal, which is sensitive to changes in cerebral blood flow and volume in addition to the rate of oxygen metabolism, in stroke patients and other groups who may exhibit impairments in cerebrovascular reactivity (CVR)—the ability of cerebral microvasculature to modulate blood flow in response to vasodilatory stimuli, such as neural activity (D'Esposito et al., 2003; Girouard and Iadecola, 2006; Lindauer et al., 2010). Such impairments may manifest as an uncoupling of neural and vascular activity that can preclude the hemodynamic response from reaching a designated threshold during a typical task-fMRI paradigm, especially when assumed to match that of young, healthy subjects (Amemiya et al., 2012; Mazzetto-Betti et al., 2010). The resulting false negatives in the BOLD signal can be misleading to both researchers and clinicians attempting to map changes in brain function after stroke. It is therefore crucial to assess the risk of neurovascular uncoupling (NVU) in stroke patients, and in turn, the validity of BOLD fMRI in this group.

Many studies have sought to assess the validity of fMRI in cerebrovascular patients, often observing a delayed, attenuated, or absent hemodynamic response to behavioral tasks with fMRI (Bonakdarpour et al., 2007; Krainik et al., 2005; Murata et al., 2006; Pineiro et al., 2002), even when a neural response is measured by other means (Amemiya et al., 2012; Binkofski and Seitz, 2004; Bonakdarpour et al., 2015; Mazzetto-Betti et al., 2010; Rossini et al., 2004). However, a majority have focused almost exclusively on the chronic stage (Bonakdarpour et al., 2015; Bonakdarpour et al., 2007; Krainik et al., 2005; Mazzetto-Betti et al., 2010; Rossini et al., 2004), several weeks to months from the stroke. Because functional imaging is often performed just days after a stroke (i.e., at the acute stage), it is critical to determine if NVU is already a significant concern at this point. Since CVR may continue to change throughout the course of stroke recovery (Beaulieu et al., 1999; Siegel et al., 2015; Widder et al., 1994), it is plausible that NVU may be only transient in stroke patients, increasing confidence in fMRI data obtained either before or after a certain risk period. Two longitudinal evaluations of the BOLD signal after stroke have supported this

* Corresponding author at: Department of Radiology, University of Wisconsin-Madison, 600 Highland Ave, Madison, WI 53792, USA.
E-mail address: rraut@wisc.edu (R.V. Raut).

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notion, suggesting that NVU risk after stroke is time-sensitive and may be minimal within the first few days of stroke (Altamura et al., 2009; Binkofski and Seitz, 2004). However, the neural variability resulting from conventional fMRI tasks presents a challenge for identifying NVU in this way, and such an approach is inherently limited to the functional region expected to be activated by the task.

In recent years, more robust means for detecting NVU risk have emerged. Specifically, breath-hold CVR mapping, which emerged as a more convenient alternative to other hypercapnic methods such as exogenous CO_2 administration, is continuing to garner attention for clinical research and application—particularly to augment functional maps obtained from presurgical tumor patients (Pillai and Mikulis, 2015; Pillai and Zaca, 2011). This non-invasive technique simply requires patients to hold their breath for short intervals inside the MR scanner. Regions of impaired CVR are not as effective in modulating blood flow in response to the induced hypercapnia and can thus be visualized as areas void of activity in the resulting fMRI maps (Pillai and Mikulis, 2015). This method has previously been used at the group level to confirm the deleterious effects of aging on CVR (Handwerker et al., 2007; Kannurpatti et al., 2010), although to our knowledge it has been implemented just twice previously for the same purpose in stroke patients (Geranmayeh et al., 2015; van Oers et al., 2010), the focus being on the subacute and chronic stages.

Thus, the goal of the present study was to quantitatively assess CVR and determine the validity of fMRI in stroke patients at the acute stage, defined in our study as less than ten days after stroke. BOLD parameters computed from a breath-hold task were compared between stroke patients and healthy controls at the group level to identify any stroke-related deficits in CVR that could give rise to NVU. These results are obtained through two separate analyses in order to compare two common approaches to accounting for the extended delay of the vascular response to hypercapnia relative to neural activity—a standard adjustment of the breath-hold model response for all subjects (standard delay) (as in (Di et al., 2013)) and an adjustment optimized on an individual basis (subject-wise delay) (as in (Bright and Murphy, 2013)).

Based on the findings of Binkofski and Seitz (Binkofski and Seitz, 2004) and Altamura et al. (Altamura et al., 2009), we hypothesized that CVR is not yet impaired at a level detectable by fMRI at the acute stage of stroke. Thus, since CVR deficits have been regularly implicated in healthy aging (D'Esposito et al., 2003; Riecker et al., 2003), we predicted that global CVR would be reduced in stroke patients compared to young controls but would not differ from older, age-matched controls. Additionally, although the degree of CVR impairment has been found to be especially pronounced in the lesioned hemisphere (Altamura et al., 2009; Binkofski and Seitz, 2004; Krainik et al., 2005; Mazzetto-Betti et al., 2010), we expected to observe no differences in CVR between the ipsilesional and contralesional hemispheres of stroke patients at this early stage.

2. Methods

2.1. Subjects

Twenty-two acute stroke patients (ages 44–75 years, mean = 59 years, 14 male) (Table 1) were included in the study, originally recruited for an ongoing longitudinal project. Inclusion criteria were at least 18 years of age, ability to provide written informed consent, and initial scan within 10 days of stroke. Exclusion criteria were history of psychiatric illness, confounding neurological disorders, drug abuse, and contraindications to MRI. Twenty-two age-matched healthy controls were also included in the study (ages 50–74 years, mean = 59, 10 male), as well as a group of 22 younger healthy controls (ages 18–27 years, mean = 22, 11 male). The study was conducted in accordance with a protocol approved by the local Health Sciences Institutional Review Board. All subjects provided written informed consent.

Table 1
Patient characteristics.

Patient	Sex	Age (years)	Time since stroke (days)	Lesion location	NIH Stroke Scale score	Treatment
1	M	75	6	C; L occipital	1	tPA + ST
2	M	69	4	L cerebellum, occipital	0	ST
3	M	74	7	C; R temporal, occipital	1	ST
4	F	44	5	C; L insula, frontal	7	ST
5	M	45	3	L cerebellum	2	ST
6	M	55	3	C; L MCA and MCA/PCA border	0	ST
7	M	62	9	C; L parietal	0	ST
8	M	58	5	C; L corticospinal tract, cerebellum	0	ST
9	F	59	7	C; R MCA	2	tPA + ST
10	M	59	4	C; R MCA	2	tPA + ST
11	M	57	3	SC; R pontine	2	ST
12	M	63	5	SC; R pontine	0	ST
13	F	47	9	C; R frontal	0	ST
14	F	58	7	C; L frontal	1	ST
15	F	59	2	C; L posterior insular, parietal	2	ST
16	F	46	0	R cerebellum	2	ST
17	M	67	5	SC; L lateral medulla	0	ST
18	M	63	3	C; R MCA	0	ST
19	F	57	6	L cerebellum	1	ST
20	M	63	2	SC; L posterior putamen	2	ST
21	M	46	3	C; R occipital	0	tPA + ST
22	F	67	5	C; R MCA	4	tPA + ST

C, cortical; SC, subcortical; L, left; R, right; MCA, middle cerebral artery; PCA, posterior cerebral artery; tPA, tissue plasminogen activator; ST, standard of care stroke treatment (in most cases consisted of antiplatelet agent (e.g., aspirin, clopidogrel), anticoagulant (e.g. heparin, warfarin), anti-hypertensive (e.g., beta blocker, angiotensin-converting-enzyme inhibitor, and/or statin (e.g., simvastatin, pravastatin)).

2.2. Data collection

All imaging data were obtained on GE 750 3T MRI scanners (GE Healthcare, Waukesha, WI) equipped with an eight-channel head coil. T1-weighted axial anatomical slices were acquired at the beginning of each session following an FSPGR BRAVO sequence (TR = 8.132 ms, TE = 3.18 ms, TI = 450 ms, 256 × 256 matrix, 156 slices, flip angle = 12°, FOV = 25.6 cm, slice thickness = 1 mm). Functional data were acquired via echo-planar T2*-weighted imaging (TR = 2.0 s, 40 slices, 90 volumes, TE = 22 ms, FOV = 22.4 cm, flip angle = 60°, voxel dimensions 3.75 × 3.75 × 4.0 mm^3).

Each breath-hold scan followed a block design consisting of four 20-s, end-expiration blocks alternating with four 20-s blocks of rest, for a total scan length of 3 min. Subjects were instructed to begin each task block with a moderate breath.

2.3. Data analysis

All preprocessing of imaging data was performed within the Analysis of Functional Neuroimages (AFNI) suite (Cox, 1996), except where noted. Subject-specific gray matter masks were created via automated segmentation of the skull-stripped anatomical volumes using FSL's FAST (FMRIB Software Library, Oxford, UK) (Zhang et al., 2001). Functional data were first aligned to the anatomical and normalized to standard Montreal Neurological Institute (MNI) space. The first four volumes were discarded to allow for steady-state imaging. Images were then resampled to 3.0 mm isotropic, despiked, volume-registered, and spatially smoothed using a 4-mm full-width at half-maximum Gaussian kernel. The time series within each voxel was scaled to percent