Hemodynamic latency is associated with reduced intelligence across the lifespan: an fMRI Dynamic Causal Modeling study of aging, cerebrovascular integrity, and cognitive ability

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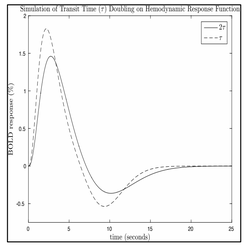
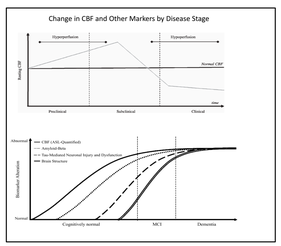
INTRODUCTION

Cerebrovascular risk factors are commonly used to identify individuals at risk for vascular dementia and other cognitive problems in clinical trials. Might augmenting cerebrovascular risk with imaging measures improve our ability to identify individuals with cognitive problems?

We assessed whether hemodynamic latency measures obtained from fMRI were associated with reduced cognitive functioning across the lifespan, holding constant demographic and cerebrovascular risk. The relationship between cerebral blood flow (CBF) and local neural activity, known as neurovascular coupling (NVC), is altered in neurocognitive disorders such as Alzheimer's disease and other dementias [1-3]. However, this relationship may be mediated by cerebrovascular risk factors such as hypertension [4], cholesterol [5], alcohol abuse [6] and smoking [7], which are also associated with cognitive ability. Moreover, mortality increases with cerebrovascular risk, so studies in elderly populations – assessing the relationship between cerebrovascular risk and cognitive ability – may be subject to survival bias [8]; the "unhealthy" high-risk population is deceased prior to the onset of dementia, leaving only "healthy" high-risk individuals for comparison with all low-risk individuals [7]. Cross-lifespan studies may better assess whether cerebrovascular risk is associated with cognitive decline by including younger populations. Using a large database from the Nathan Kline Institute, we tested the hypothesis that latency of the hemodynamic response function (HRF) would be associated with reduced cognitive functioning, above and beyond all other demographic and cerebrovascular risk factors.

METHODS





The HRF is the regional Blood Oxygenation Level Dependent (BOLD) response generated from a brief peripheral stimulus, created through a sequence of vascular and metabolic dynamics [9-11], providing regional models of NVC. In the HRF modeling the BOLD signal arises from a change in the total deoxyhemoglobin content of an element of tissue. The deoxyhemoglobin content in turn depends on the dynamics of cerebral blood flow (CBF), cerebral blood volume (CBV), and cerebral oxygen metabolism (CMRO2). Parameters governing the HRF are estimable through Dynamic Causal Modeling (DCM) [13]. The latency parameter of the HRF, τ, is most closely tied to the concept of the speed of the response and the time to reach the response peak.

METHODS (Continued)

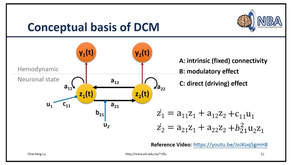
	Female		Male	
	Mean	sd	Mean	sd
N	251	-	136	-
Transit V1 L	0.02	0.13	0.02	0.13
Transit V1 R	0.04	0.14	0.03	0.13
Transit V3 L	-0.02	0.12	0.001	0.12
Transit V3 R	0.001	0.12	0.001	0.11
Smoker	15%		29%	
Any Heavy Alcohol Use	51%		55%	
Age	50.86	18.4	44.71	20.34
Years of Education	15.67	2.28	15.25	2.53
Socioeconomic Score	47.15	12.07	44.36	14.15
Heart Attack	0.40%		3%	
Coronary Artery Disease	1%		4%	
Heart Valve Disease	3%		1%	
High Cholesterol	34%		36%	
High Blood Pressure Hypertension	24%		23%	
Irregular Heartbeat Arrhythmia	13%		4%	
Diabetes type 2	7%		4%	
BMI	27.7	6.13	27.67	4.8
BMI: obese	55%		65%	
Any Cardiac Disorder	17%		13%	

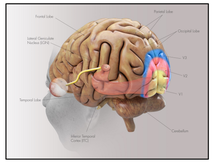
Table 1: Demographics of NKI subjects. The Nathan Kline Institute, Rockland Sample (NKI-RS) sample is an ongoing initiative aimed at creating a large-scale (N>1000) community sample across the lifespan, taken from subjects residing in Rockland County, NY [34]

Subjects were scanned using fMRI in a blocked design using a checkerboard stimulus consisting of three repetitions of a 20s fixation block and a 20s flickering checkerboard block. This task required minimal cognitive demand and activates the visual cortex- one of the final regions to deteriorate in Alzheimer's disease. Thus, the visual cortex is the optimal fMRI brain region to capture hemodynamic changes unrelated to cognition or structural pathology.

fMRI pre-processing was performed with SPM12 (Wellcome Centre for Human Neuroimaging, London, UK) using standard SPM procedures. Single subject analyses were performed using the General Linear Model. Inferences about Group responses were adjusted from comparisons using Random Field Theory. Four regions of the visual cortex which showed strong activations were used for the DCM model, where the optimal model was selected from sixteen candidate models using Bayesian Model Selection.

Following DCM estimation, the latency parameters from the four regions of the visual cortex were extracted and mapped to intelligence (WASI-II) using a general linear model.





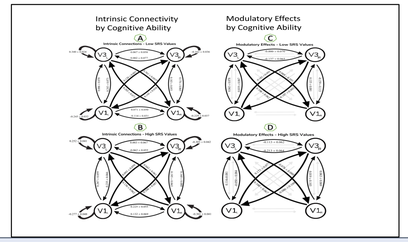
METHODS (Continued)

Dynamic causal modeling was used to estimate the hemodynamic response function in the left and right V1 and V3-ventral regions of the visual cortex in response to a simple checkerboard block design stimulus with minimal cognitive demands. The hemodynamic latency (transit time) in the visual cortex was used to predict general cognitive ability (Full-Scale IQ), controlling for demographic variables (age, race, education, socioeconomic status) and cerebrovascular risk factors (hypertension, alcohol use, smoking, high cholesterol, BMI, type 2 diabetes, cardiac disorders).

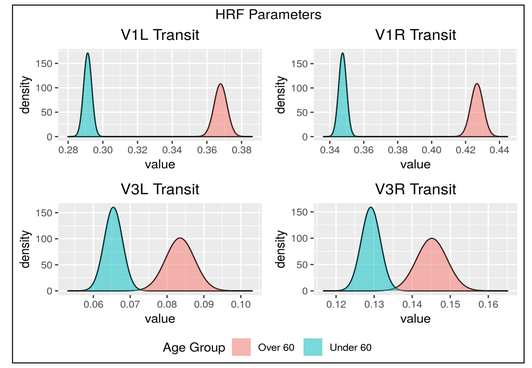
RESULTS

Increased hemodynamic latency in the visual cortex predicted reduced cognitive function ($p<0.05$), holding constant demographic and cerebrovascular risk. Increased alcohol use was associated with reduced overall cognitive function (Full Scale IQ 2.8 pts, $p<0.05$), while cardiac disorders (Full Scale IQ 3.3 IQ pts; $p<0.05$), high cholesterol (Full Scale IQ 3.9 pts; $p<0.05$), and years of education (2 IQ pts/year; $p<0.001$) were associated with higher general cognitive ability. Increased hemodynamic latency was associated with reduced executive functioning ($p<0.05$) as well as reductions in verbal concept formation ($p<0.05$) and the ability to synthesize and analyze abstract visual information ($p<0.01$).

Within late middle-aged adults aged 50-65, we compared connectivity between low and high cognitive functioning individuals. Cognitive functioning was measured using the WASI-II Similarities Raw Score (SRS) subtest. The DCM model included four regions: Primary Visual (V1) left and right cortex, and higher-order visual (V3) left and right cortex. Cross-hemispheric effective connectivity differed between high functioning and low-functioning older adults ($p<0.05$) on the WASI-II Similarities Raw Score (SRS), with the V3 regions showing significant differences in both effective connectivity and modulatory effects ($p<0.05$). Panel A: Intrinsic connectivity by low SRS. Panel B: Intrinsic Connectivity by high SRS. Panel C: Effective connectivity by low SRS. Panel D: Effective connectivity by high SRS. Group-level estimates for the effective connectivity and modulatory effects for the C1-M5 model. Labels for the edges are of the form (estimated) mean +/- (estimated) standard deviation.



RESULTS (Continued)



Using Bayesian parameter averaging, the posterior distributions of the transit and decay parameters for each group showed differences between the older (>=60) and younger (<60) age groups. The transit time (hemodynamic latency) was increased for older subjects. Because transit and latency parameters were highly correlated within each subject, only the transit parameters were evaluated.

CONCLUSIONS

Our results suggest that increased hemodynamic latency in the healthy visual cortex is associated with reduced cognitive ability. The visual cortex is among the last regions to deteriorate in Alzheimer's disease as defined by [33]. Yet, effective connectivity changes have been shown in the visual cortex of early Alzheimer's disease patients [17]. Decreased processing speed and executive functioning are the hallmark changes associated with healthy aging; with EEG markers of cognitive ability also changing with age [61]. These patterns of cognitive changes are also characteristic of neurocognitive disorder due to vascular pathology.

The flickering checkboard fMRI paradigm does not involve higher-order cognitive processing, since it is a simple visual stimulus. The focus on the visual cortex in this study helps dissociate the effects of neurodegeneration in AD with hemodynamic differences. The latency of the HRF in the visual cortex establishes that CBF changes are associated with reduced cognitive ability in areas unlikely to be experiencing neurodegeneration. It is likely that these HRF deficits may be found elsewhere in the brain and may be fundamental to cognition.

ACKNOWLEDGEMENTS

Supported by the Burroughs Wellcome Fund and the National Institutes of Health (NIH) – (National Institute of Mental Health UL1DE019580, R01MH101478, PL1MH083271 to RB, R03MH106922 to RB and AA; by the National Institute on Aging (NIA) K25AG051782 to AA, and by a Research Supplement to Promote Diversity in Health-Related Research Award U01 AG052564-01 from NIA to MDS.

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