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

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## Abstract

Changes in neurovascular coupling are associated with both Alzheimer's disease and vascular dementia in later life, but this may be confounded by cerebrovascular risk. We hypothesized that hemodynamic latency would be associated with reduced cognitive functioning across the lifespan, holding constant demographic and cerebrovascular risk.

In 387 adults aged 18-85 (mean = 48.82), 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).

Increased hemodynamic latency in the visual cortex predicted reduced cognitive function ($p<0.05$), holding constant demographic and cerebrovascular risk. Increased alcohol use was

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Compliance with Ethical Standards:

The Authors have declared that there are no conflicts of interest in relation to the subject of this study. The dataset was originally collected at the Nathan Kline Institute (NKI). All NKI subjects provided written informed consent after receiving a complete description of the study; this study was approved by the Institutional Review Board and adheres to US Federal Policy for the Protection of Human Subjects. Institutional Review Board Approval was obtained for this project at the Nathan Kline Institute (Phase I #226781 and Phase II #239708) and at Montclair State University (Phase I #000983A and Phase II #000983B).

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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 ($p<0.01$).

Hemodynamic latency is associated with reduced cognitive ability across the lifespan, independently of other demographic and cerebrovascular risk factors. Vascular health may predict cognitive ability long before the onset of dementias.

## Introduction

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 (Wierenga, Dev et al. 2012, Østergaard, Aamand et al. 2013, Wierenga, Hays et al. 2014). However, this relationship may be mediated by cerebrovascular risk factors such as hypertension (Nobili, Rodriguez et al. 1993), cholesterol (Notkola, Sulkava et al. 1998), alcohol abuse (Anttila, Helkala et al. 2004) and smoking (Chang, Zhao et al. 2012), 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 (Johnston and Hauser 2010); 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 (Chang, Zhao et al. 2012). 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.

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 (Friston, Mechelli et al. 2000, Buxton, Uludağ et al. 2004, Wan, Riera et al. 2006), 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 ($CMRO_2$). The model used here was developed by (Friston, Mechelli et al. 2000) by incorporating the earlier Balloon Model (Buxton, Wong et al. 1998) as a model for how the BOLD signal depends on CBF, CBV and $CMRO_2$, and adding a model for how neural activity generates a time-dependent CBF response. The Balloon model component treats CBV and the O2 extraction fraction as functions of CBF, with the former chosen to match empirical relationships, and the latter based on an analytic expression developed in (Buxton, Wong et al. 1998) for the situation in which the extraction is unidirectional (i.e., all $O_2$ extracted from the capillary is metabolized). In this part of the model the parameter $\tau$ defines the temporal scale of the BOLD response (e.g., the temporal response to a step change in flow), and $\tau = V_0/F_0$,

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where $V_0$ is the resting CBV and $F_0$ is the resting CBF. The second component introduced in the Friston model is a time-dependent flow-inducing signal *s*, with *s* increased by neural activity, and with the rate of change of CBF proportional to *s*.

Parameters governing the HRF are estimable through Dynamic Causal Modeling (DCM) (Friston, Harrison et al. 2003). DCM is a generative network model that estimates coupling within and among regions of interest in the brain, and how regions respond to stimuli across time. Because DCM uses a generative (i.e., forward) model, model inversion provides posterior probabilistic estimates of the parameters governing the regional HRF. These parameters are estimated using variational Bayes based upon the Laplace assumption. In DCM's haemodynamic model, $\tau$ is the mean transit time of blood; i.e., the average time blood takes to traverse the venous compartment. The empirical value $\tau$ estimated from fitting to the model could well include other effects that are not explicitly modeled (such as slower dynamics of CBV or $CMRO_2$ compared to CBF. The latency parameter of the HRF, $\tau$, has the effect illustrated in Figure 1, of both changing the overall speed of the response and affecting the relative magnitudes of the initial positive BOLD signal change and the negative response, following the end of the stimulus (post-stimulus undershoot). The transit time is most closely tied to the concept of the speed of the response and the time to reach the response peak.

Taken together, the model connects a dynamic change in neural activity to the dynamic change in the BOLD signal. Because the model is based on a number of assumptions, the fitted parameters are best treated as empirical values that represent the lumped effects of the true physiology being modeled in a simple way. Many of the assumptions, such as the relationships between the O2 extraction fraction and CBF or between CBV and CBF, affect the amplitude of the BOLD signal, rather than the timing. Thus, parameter estimates of the HRF are a representation of multiple processes involved in NVC, rather than a single physiological measure.

NVC is altered in the visual cortex in Alzheimer's disease (AD) (Mentis, Horwitz et al. 1996). The visual cortex, perfused by the posterior cerebral artery, contains the highest density of neurons in the cortex (Leuba and Kraftsik 1994). Changes in posterior cerebral blood flow were previously mapped to aging, and were associated with fibrinogen and indicators of carotid atherosclerosis (Claus, Breteler et al. 1998). Previously, effective connectivity changes in the visual cortex were identified using DCM in early Alzheimer's disease (Rytsar, Fornari et al. 2011) using a blocked checkerboard stimulus. Changes in the hemodynamic response function's amplitude were also seen between older and younger subjects with a flickering checkerboard task, suggesting this stimulus is sensitive to age-related BOLD changes (Buckner, Snyder et al. 2000, Ances, Liang et al. 2009). Age-related HRF changes outside the visual cortex in the motor and auditory cortices suggest that the HRF evolves across the lifespan (West, Zuppichini et al. 2019).

The association between NVC and cognitive ability may be mediated by cerebrovascular risk, since cerebrovascular risk factors alter cerebral blood flow. CBF is reduced in patients with untreated hypertension compared to those with treated hypertension (Nobili, Rodriguez et al. 1993). Hypertension is associated with reduced cognitive performance (Elias, Wolf

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et al. 1993, Robbins, Elias et al. 2005), and mid-life hypertension increases the risk of cognitive impairment in older age (Launer, Masaki et al. 1995, Birkenhäger, Forette et al. 2001). However, hypertension treatment alone does not decrease the risk of dementia in older adults (McGuinness, Todd et al. 2009, Novak and Hajjar 2010). Other clinical measures also support the association between vascular health and cognitive ability. High cholesterol affects cognitive domains differently, with increases seen in Block Design, but decreases in crystallized intelligence using the Wechsler Adult Intelligence Scale, Revised (WAIS-R) (Muldoon, Ryan et al. 1997). High cholesterol increases the risk for atherosclerosis (de la Torre 2012), which is also a risk factor for dementia (Dolan, Crain et al. 2010). High midlife total serum cholesterol is associated with an increased risk of AD and any dementia, but not vascular dementia (Anstey, Lipnicki et al. 2008, Solomon, Kivipelto et al. 2009). Total serum cholesterol decreased in those who subsequently developed AD (Notkola, Sulkava et al. 1998), with potential decreases in blood pressure also preceding disease onset (Breteler 2000).

Analyses of cerebrovascular risk and cognitive ability in elderly cohorts may be confounded by competing risk and survival bias (Chang, Zhao et al. 2012), where subjects with higher cerebrovascular risk are likely to die before dementia onset. Given the changes in NVC and CBF associated with neurocognitive disorders in older adults, we hypothesized that age-abnormal NVC may predict reduced cognition across the lifespan, while controlling for other cerebrovascular risk factors. Because multiple areas of the brain are essential for the functional integration that underwrites higher cognitive function, this hypothesis was tested using a passive visual stimulus (flickering checkerboard), which requires minimal cognitive effort and has no known relation to cognitive performance. The occipital lobe, activated by visual stimuli, is one of the first areas of the brain to myelinate – and one of the final areas to degenerate in Alzheimer's disease – which helps to decouple the impact of neurodegeneration and cerebral hemodynamics in aging populations (Braak, Alafuzoff et al. 2006). In 387 adults aged 18-85, we used DCM to estimate the HRF in the visual cortex in response to a flickering checkerboard stimulus; similar to the approach of Rytsar et al. (Rytsar, Fornari et al. 2011). Ances et al. previously found that the duration of the HRF undershoot was increased in elderly populations – but not the magnitude of this undershoot (Ances, Liang et al. 2009), suggesting that hemodynamic latency may change with age. Collectively, we asked whether hemodynamic latency predicts global and specific cognitive abilities, independent of all other demographic and cerebrovascular risk factors, across the lifespan. Our results suggest that latency in the hemodynamic response function predicts reduced cognitive ability, after holding constant all other cerebrovascular and demographic factors.

## Methods:

### 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 (Nooner, Colcombe et al. 2012). All subjects provided written informed consent after receiving a complete description of the study; this

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study was approved by the Institutional Review Board and adheres to US Federal Policy for the Protection of Human Subjects. Subjects in NKI were excluded for any of the following criteria: history of stroke (ischemic or hemorrhagic), severe psychiatric illness (bipolar disorder, schizophrenia disorder, schizoaffective disorder), severe developmental disorders (autism spectrum disorders, intellectual disabilities), current suicidal or homicidal ideation, severe cerebral trauma (stroke, moderate to severe traumatic brain injury, ischemic attack in the past two years), severe neurodegenerative disorders (Parkinson's disease, Huntington's Disease, dementia), a history of substance dependence in the past two years (with an exception for cannabis), a lifetime history of psychiatric hospitalization, current pregnancy, MRI contraindications, insufficient fMRI visual cortex activation, excessive measured fMRI motion > 3 mm, missing clinical or medical history data, and insufficient scan coverage. After exclusion, there remained 387 subjects who had both full clinical information and suitable fMRI and MRI scans for subsequent neurocognitive analyses, described in more detail in the Supplementary Table 1 in the Appendix.

Subjects completed a medical history exam and a series of functional and structural MRI scans, described further in (Nooner, Colcombe et al. 2012) in either a 1 or 2-day period. Subjects were screened for alcohol use with the NIDA quick screen (Wu, McNeely et al. 2016), and for nicotine dependence using the Fagerstrom Test for Nicotine Dependence (Heatherton, Kozlowski et al. 1991). Additionally, neuropsychological batteries were administered including the Wechsler Abbreviated Scale of Intelligence (WASI-II; (Stano 2004)), the Delis-Kaplan executive function system (DKEFS) (Sue Baron 2004), and the Rey auditory verbal learning test (RAVLT; (Schmidt 1996)). These three protocols were chosen for their sensitivity to measures cognitive abilities typically affected by vascular health, and are described further in the Appendix. Full demographic and clinical assessment summaries are provided in the Appendix: Table 1.

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. Scans were repeated using two different TRs: 1400 ms. The following parameters were used: TR = 1400 ms; TE = 30 ms; flip angle = 65 deg; voxel size = 2 x 2 x 2 mm isotropic; number of slices = 64. TR = 645 ms; TE = 30 ms; flip angle = 60 deg; voxel size = 3 x 3 x 3 mm. isotropic; number of slices = 40. Anatomical T1 images were scanned using MPRAGE (magnetization-prepared rapid acquisition with gradient echo) sequence with the following parameters: TR = 1900 ms; TE = 2.52 ms; flip angle = 90 degrees; voxel size = 1 x 1 x 1 mm (isotropic).

fMRI pre-processing was performed with SPM12 (Wellcome Centre for Human Neuroimaging, London, UK) using standard SPM procedures (Penny, Friston et al. 2011): realignment to correct for head movement, normalization to MNI space and convolution with an isotropic Gaussian kernel (FWHM=9 mm) to increase the signal to noise ratio. Single subject analyses were performed using the General Linear Model, removing signal drift with a high-pass filter. Statistical parametric maps for the checkerboard contrast (i.e., responses to visual stimulation) were obtained using the appropriate contrast under a general (convolution) linear model. Inferences about Group responses were adjusted from comparisons using Random Field Theory. Visually responsive regions were identified using

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clusters with a height threshold of $p<0.005$ (t-test) and extent threshold $k>30$ contiguous voxels.

### Dynamic Causal Modeling:

Inversion of models in DCM permits inference on several regional parameters that shape the haemodynamic response. To invert a DCM model, the free energy is minimized to maximize the model evidence. Four regions of interest were selected for further analyses based on the SPM analyses identifying regional responses to checkerboard stimulus: V1 Left, V1 Right, V3-ventral Left, and V3-ventral Right. These regions also have established roles in processing basic visual stimuli (Lang, Bradley et al. 1998, Smith, Greenlee et al. 1998, Dumoulin and Wandell 2008, Rytsar, Fornari et al. 2011) with V3 regions providing higher-order processing than the primitive V1 region. Using the Wang visual cortex atlas (Wang, Mruczek et al. 2014), non-overlapping masks of these four regions were created and then applied to each subject's SPM. Regional responses were summarized – for subsequent DCM analysis – with the first principal component of all voxel time series within a sphere of 4 mm radius, centered on the individual local SPM maxima within each atlas mask.

The visual stimulus presented follows the work of (Rytsar, Fornari et al. 2011), which used a simple flickering checkerboard in a block design. Sixteen competing models differing by effective connectivity were compared using both Bayesian model selection and random-effects Bayesian model selection, detailed in Figure 2. Driving or visual inputs were restricted to the early visual regions. For completeness, Bayesian model selection (BMS) was performed using two approaches: (i) fixed effects BMS; namely, pulling the log-model evidence (i.e., the negative free energy) over subjects for each model (Friston, Harrison et al. 2003) and (ii) random effects BMS (Stephan, Penny et al. 2009, Rigoux, Stephan et al. 2014). After selecting the optimal connectivity model, five candidate models for additional modulatory effects were considered; where modulatory effects represent the interaction between the effective connectivity and the driving inputs. These modulatory effects model the effects of driving inputs (i.e. visual stimulation) on connectivity among regions – in addition to direct effects on regional activity. Bayesian model selection of the best modulatory model used the same approach above.

We tested our hypotheses by using subject-specific estimates of haemodynamic parameters in the four regions (V1 Left, V3 Left, V1 Right, V3 Right) from the DCM as independent variables to predict cognition (dependent variable), while controlling for both demographic and cerebrovascular risk factors. The variable of interest was the latency of the HRF. In DCM's haemodynamic model, $\tau$ is the mean transit time of blood; i.e., the average time blood takes to traverse the venous compartment. The transit time corresponds to the ratio of resting blood volume $V_0$ to resting cerebral blood flow $F_0$: $\tau = V_0/F_0$. This is the model parameter most closely tied to the concept of the speed of the response and the time to reach the response peak.

The visual cortex was the main region of interest because it has limited involvement in higher-order cognitive processes and is the last region to be affected by Alzheimer's disease, making it an optimal region for identifying how changes in the HRF may predict cognitive changes independent of other neurodegenerative processes. Our primary hypothesis was

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that longer hemodynamic latency (transit time) in visual regions would be associated with lower cognitive ability, after adjusting for all other demographic and cerebrovascular risk factors. Because of the sampling resolution, other hemodynamic-specific DCM methods were not feasible (Heinzle, Koopmans et al. 2016). The WASI full-scale IQ composite score was used as the primary outcome measure of global cognitive ability, because it provides a comprehensive average over several cognitive domains. To avoid performing multiple comparisons within multiple cognitive domains, a single outcome measure (full-scale IQ) tested general cognition as the primary hypothesis. Years of education was included as a covariate to control for pre-morbid functioning.

This hypothesis was tested using a general linear model in R. All four HRF latency parameters estimated from each subject's fMRI scan were included in a single model, to predict cognitive ability while holding constant their demographics and cerebrovascular risk. Demographic covariates – used to explain global cognitive ability – included age, gender, race, socioeconomic status, years of education, and an interaction effect between race and socioeconomic status. Cerebrovascular risk factors included hypertension, BMI, smoking status, heavy alcohol use, high cholesterol, Type 2 Diabetes, and an indicator variable for "cardiac disorders", including history of any of the following conditions: history of heart attack, coronary artery disease, heart valve disease, and arrhythmia. Subjects with a history of stroke were excluded from the analysis. Heavy alcohol use was defined as having *any* positive number of heavy drinking days according to the NIDA- Quick screen question: "In the past year, how often have you used alcohol? For men, 5 or more drinks a day. For women, 4 or more drinks a day."

Following the test of the global hypothesis, posthoc analyses assessed which specific cognitive domains are most associated with hemodynamic latency, since the WASI captures multiple domains of intelligence. The demographic, cerebrovascular, and regional hemodynamic parameters were used to predict domain measures of executive functioning, verbal fluency, and matrix reasoning as measured by the WASI subscales, DKEFS, and RAVLT described in the Appendix, Table 2. When available, both raw and scaled scores were tested to assess the consistency of our findings.

Next, we assessed whether the parametric estimates of hemodynamic latency changed with age, following the findings of (West, Zuppichini et al. 2019). Bayesian parameter averaging (BPA) was used to compute the transit time for each region of interest in young and old subjects. BPA provides posterior estimates of group means and variances for transit and decay parameters, for each region, weighted by the precision of subject specific estimates. Subjects with suitable fMRI scans and age information (n=599) from the larger sample were split into those with age greater or equal to (n=168) and less (n=431) than 60 to evaluate BPA of hemodynamic latency. This sample includes those subjects previously omitted for incomplete neurocognitive assessments. The BPA posterior over group means provides a direct Bayesian characterization of group effects, in terms of Bayesian credible intervals.

Finally, we replicated the earlier findings of (Rytsar, Fornari et al. 2011), which identified weakened effective connectivity (and its modulation) in early Alzheimer's disease. Within later middle-aged adults aged 50-65 who did not have any clinical diagnoses of AD, we

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assessed whether effective connectivity differed between high cognitive performers and low cognitive performers. The SRS was selected as the measure of cognitive performance, since it was the domain of the WASI best predicted by the hemodynamic latency in the entire population. Within the 50-65 age range, subjects were partitioned into two groups according to whether they were in the bottom or top twentieth percentile for Similarities Raw Score (SRS) within the sample for subjects of that age. The resulting sample sizes were n=20 for small SRS values (5 male, 15 female) and n=21 for high SRS values (5 male, 16 female). Group effects were tested using a three-way mixed effects ANOVA model for both the effective connections and modulatory effects, within the model selected by BMS. This approach is similar to the Parametric Empirical Bayes Approach by permitting to characterize inter-subject variability in neural circuitry(Zeidman, Jafarian et al. 2019). Factors included in this model included group (high and low SRS values), hemisphere of the connection (L/R), whether or not the connection crossed a hemisphere (Y/N), and the regional topography of the connection (V1 ↔ V3, V1 ↔ V1, V3 ↔ V3 for intrinsic connections; V1 ↔ V3, V3 ↔ V3 for modulatory effects). The mixed-effects ANOVA model corrects for multiple comparisons by treating the subject as a random effect, with other covariates modeled as fixed effects.

## Results

Fixed and random effects Bayesian model selection yielded consistent results for selecting the optimal connectivity for the DCM model: for both of these approaches, Model C1 was optimal. After selection of the optimal effective connectivity model, modulatory models were also compared. Both fixed and random effects BMS yielded M5 as best and M4 as second best. Thus, the combined model of C1-M5 was selected to provide estimates the of hemodynamic parameters, as shown in Figure 2.

Model A variants included bilateral connections between primary visual regions (V1), which were omitted in Model B. Model C variants all included bilateral cross-hemispheric connections between primary visual areas, but also contained both unilateral and bilateral cross connections between both regions and hemispheres (e.g. V1L→ V3R). Model D variants similarly investigated cross-connections between regions and hemispheres, but omitted the bilateral primary visual connections amongst V1 regions. Model 1 variants were exclusively bilateral connections, while Model 2 variants all lacked bilateral connectivity between higher-order (V3) visual areas. Model 3 families included connectivity from V3R to V3L, while Model 4 families included connectivity from V3L to V3R.

The global hypothesis was that hemodynamic latency would predict reduced global cognition. The analysis of between-subject effects using a general linear model found that hemodynamic latency in the V3 Left and V3 Right regions were associated with reduced general cognitive ability (full-scale IQ composite score, $p<0.05$), as shown in Table 1. Alcohol use was also associated with reduced IQ (2.8 pts, $p<0.05$) while cardiac disorders (3.3 IQ pts; $p<0.05$), high cholesterol (3.9 pts; $p<0.05$), and years of education (2 IQ pts/year; $p<0.001$) were associated with higher general cognitive ability as shown in Table 1. These individual factors are interpreted holding constant all else, including age and BMI. Posthoc analyses showed that for the V3 region, specific domain changes were found

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within WASI-II Similarities Raw Score ($p<0.001$), D-KEFS Category Fluency, Tower (Total Achievement Score), Trails Test (Motor Speed, Letter Sequencing) and Word Context, and RAVLT (Delay Recall- total correct), as shown in the Appendix.

Bayesian parameter averaging (BPA) was used to characterize age-related differences in transit and decay parameters for each region of interest. Subjects with suitable fMRI and age data (n=599) from the larger sample were partitioned into those with age >= 60 (n=168) and age <60 (n=431). This sample is larger than the primary analyses because it includes subjects who may have had incomplete neuropsychological assessments. The BPA estimates group means (and variances) for transit and decay parameters for each region. As shown in Figure 3, age-related differences were most marked for the transit and decay parameters in both left and right V1, with adults above the age of 60 exhibiting larger transit and decay values than younger subjects. It can be clearly seen that the older subjects have a group mean that is outside the 95% credible interval for the younger subjects (and *vice versa*). This suggests that the group means are likely to differ, but there was overlap between subject groups suggesting it is not possible to reliably estimate a subject's age based upon their measured transit parameters.

To replicate the earlier findings of (Rytsar, Fornari et al. 2011), we additionally assessed whether effective connectivity (and its modulation) differed between high and low cognitive performers using a mixed-effects ANOVA in late-middle-aged adults (50-65-year-olds) to control for repeated measures (connectivity estimates) for each subject. Effective connectivity involving V3 showed a significant effect of group (estimated effect −0.142, $p < 0.005$), and the cross hemisphere connectivity showed a significant interaction with group (estimated effect −0.123, $p < 0.05$). A chi-squared test was performed to confirm that the addition of interaction effects was significant ($p < 0.03$). For modulatory effects, the V3 connections showed a significant effect of group (estimated effect −0.122, $p < 0.02$). Full model parameters are provided in Figure 4.

## Discussion:

Altered neurovascular coupling (NVC) is one of several possible pathways connecting cardiovascular risk factors to cognitive decline later in life (Novak 2012). Our study found that increased hemodynamic latency – as measured in the visual cortex – may be associated with reduced cognition in a healthy sample across the lifespan. Specifically, using hemodynamic parameters from V1 and V3 regions that best explain the response to a flickering checkboard, we confirmed that increased hemodynamic latency predicted reduced general cognitive ability, above and beyond all other demographics and cerebrovascular risk factors; including diabetes, hypertension, and hyperlipidemia. Increased hemodynamic latency in the V3 Left and V3 Right regions predicted reduced overall cognitive ability (WASI-II; IQ measurement). This global test suggests that vascular health impacts general cognitive ability measures (WASI Full-scale IQ).

Following testing of the global hypothesis, specific cognitive domains were also tested. For both the V1 (primary visual cortex) and V3 region (visual association area), specific cognitive domains were also sensitive to changes in hemodynamic responses.

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Hemodynamic latency in V1 predicted cognitive changes in visuomotor planning, organization and sequencing (DKEFS Tower, and verbal memory (RVALT Delay Recall). Hemodynamic latency in V3 predicted cognitive changes in abstract verbal reasoning (WASI-II Similarities), and semantic verbal fluency (DKEFS Category Fluency). These tests, associated with fluid intelligence, do not establish functional specificity, but suggest that the general cognitive changes established in the global hypothesis may be associated with deficits in more narrow domains. Fluid intelligence is more susceptible to neurological damage than crystallized intelligence, with other studies associating neurocognitive disorders with changes in cerebral blood flow.

Cerebral blood flow differences have been observed with impaired cognitive functioning (Buckner, Snyder et al. 2000) and increased age (Buckner, Snyder et al. 2000, Riecker, Grodd et al. 2003, Gröschel, Terborg et al. 2007, Ances, Liang et al. 2009), with hemodynamic changes preceding cognitive decline (Wierenga, Dev et al. 2012, Østergaard, Aamand et al. 2013, Wierenga, Hays et al. 2014). NVC may be altered in hypertension, ischemic stroke, and Alzheimer's disease, as discussed in Girouard et al. (Girouard and Iadecola 2006). Disruption in NVC has been found throughout the brain following lacunar stroke (Pineiro, Pendlebury et al. 2002) and in patients with disrupted cerebrovascular reserve capacity due to intra/extracranial stenosis (Hamzei, Knab et al. 2003). Stroke is a risk factor for both Alzheimer’s disease (Zhou, Yu et al. 2015) and other dementias (Kuźma, Lourida et al. 2018). Subjects with Mild Cognitive Impairment – who also had CBF deficits – converted more rapidly to Alzheimer’s disease (Hirao, Ohnishi et al. 2005), while other work suggests APOE-4 genotype and vascular health may be interacting risk factors for cognitive decline (Jarvik, Wijsman et al. 1995, Notkola, Sulkava et al. 1998, Breteler 2000, Evans, Emsley et al. 2000, Evans, Hui et al. 2004, Anstey, Lipnicki et al. 2008, Solomon, Kivipelto et al. 2009).

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 (Braak, Alafuzoff et al. 2006). Yet, effective connectivity changes have been shown in the visual cortex of early Alzheimer’s disease patients (Rytsar, Fornari et al. 2011). Decreased processing speed and executive functioning are the hallmark changes associated with healthy aging; with EEG markers of cognitive ability also changing with age (Trammell, MacRae et al. 2017). These patterns of cognitive changes are also characteristic of neurocognitive disorder due to vascular pathology.

Studies have shown increased levels of white matter hyperintensities in periventricular and subcortical areas, as well as frontal areas (Bahrani, Powell et al. 2017), yet few studies have indicated that cerebral blood flow in the visual cortex may be associated with decreased function in cognitive tasks typically associated with higher-order cortices. Our 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

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deficits may be found elsewhere in the brain and may be fundamental to reduced cognition. Investigating whether such changes are global is a direction for future research.

Other cardiovascular risk factors were found associated with increased and decreased cognition. Because we relied on patient medical history, it is possible that recall bias influences some of our findings- such as cardiovascular diagnoses and high cholesterol history being positively associated with intelligence. Given that low-income or low-educational level individuals are more likely to have undiagnosed medical disorders. This confound was tested by evaluating whether a high cholesterol diagnoses differed by education level using a 2-sample t-test, evaluated separately within the younger (18-65 years) and geriatric (65+) cohort. These results were negative, suggesting that diagnostic disparity did not drive this finding. Additionally, our models controlled for education and socioeconomic status. Rather, others have reported a drop in serum cholesterol associated with dementia onset (Notkola, Sulkava et al. 1998). Future work will investigate whether laboratory testing of serum cholesterol and patient-reported medical history may predict similar changes in cognition.

## Limitations and Future Studies

There are several limitations to this study. The hemodynamic latency is highly correlated with other hemodynamic response parameters such as decay in the BOLD signal model (Figure 5), and it is possible these may also be associated with cognition. It is important to remember that detailed parameters related to the physiology underlying the BOLD response cannot be determined reliably from just the BOLD signal itself – without additional measurements of that physiology, such as blood flow measured with arterial spin labeling (Friston, Preller et al. 2017). Arterial spin labeling is commonly used to measure cerebral perfusion, yet has poor temporal resolution making it suboptimal for evaluating NVC. Additionally, we were not able to control for caffeine or alcohol intake the day of the scan, and there was limited information provided on medications subjects were receiving. Finally, although subjects with *any* neurodegenerative disease (Parkinson's disease, Huntington's disease, dementia) or brain injury (TBI, stroke, ischemic attack) were excluded from this analyses, we did not measure the impact of cortical atrophy or white matter damage. Given that complications of cortical atrophy such as neurological, cognitive (dementia) and psychiatric diseases were exclusion criteria from this study, it is unlikely that our findings are driven by atrophy. Similarly, white-matter damage (leukoaraiosis) is associated with cerebrovascular risk which was also controlled for in this analyses.

The patterns observed in the visual cortex associated with reduced cognitive ability may be different elsewhere, as other DCM modeling work fusing fMRI and MEG estimations has suggested the neurovascular coupling mechanisms are region-specific (Jafarian, Litvak et al. 2019). Nevertheless, analysis with a multi-parameter BOLD model can track subtle differences in the responses across a population through variations in the estimated parameters – and here we found that the latency $\tau$ was useful in separating the studied populations. Because of the nature of the model, however, a significant increase of $\tau$ in one group could be due to an overall slowing down of the BOLD response (e.g., delayed time to peak) or to a reduced post-stimulus undershoot relative to the positive signal (see Figure

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1). That is, underlying changes in the physiology that would lead to either of these observed effects on the BOLD signal could lead to a similar finding of increased $\tau$. Alternative approaches to estimating these parameters such as stochastic metabolic/hemodynamic models are an area for future research (Sotero, Trujillo-Barreto et al. 2009).

Similarly, hemodynamic changes may be a mediator for an unobserved external factor; the relationship of hemodynamic latency with cognition may not be causal. A large number of subjects had incomplete neurocognitive assessments. It is therefore possible that these data were not missing at random and excluding subjects with incomplete data may have introduced some bias. Finally, although this study observed similar relationships between older and younger cohorts, it is possible that the competing risk bias our findings. The missing cohort of high-cardiovascular risk individuals – who passed before study enrollment – may have had different relationships than the subjects who survived until old-age.

In summary, in functional MRI (fMRI) studies of aging and disease, the observed blood-oxygen-level dependent (BOLD) signal is assumed to be a convolution of the neuronal stimuli and a hemodynamic response function (HRF). The analyses using a blocked checkerboard stimulus demonstrates that the hemodynamic latency, as measured by the fMRI HRF transit parameters, may change both with age and cognitive ability, above and beyond all other demographic and stroke risk factors including high cholesterol. Given that the checkerboard task is entirely passive and not cognitively demanding, our results suggest that hemodynamic latency measures were associated with vascular and not cognitive processes. Moreover, it suggests that hemodynamic latency may provide an additional metric to complement ASL for assessing how changes in blood flow may affect current and future cognitive ability. Collectively, these findings suggest that vascular health and cognitive health may share underlying risk factors across the lifespan.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Data Availability Statement:

The data that support the findings of this study are openly available in Collaborative Informatics and Neuroimaging Suite (COINS) at https://coins.trendscenter.org, reference number NKI-RS.

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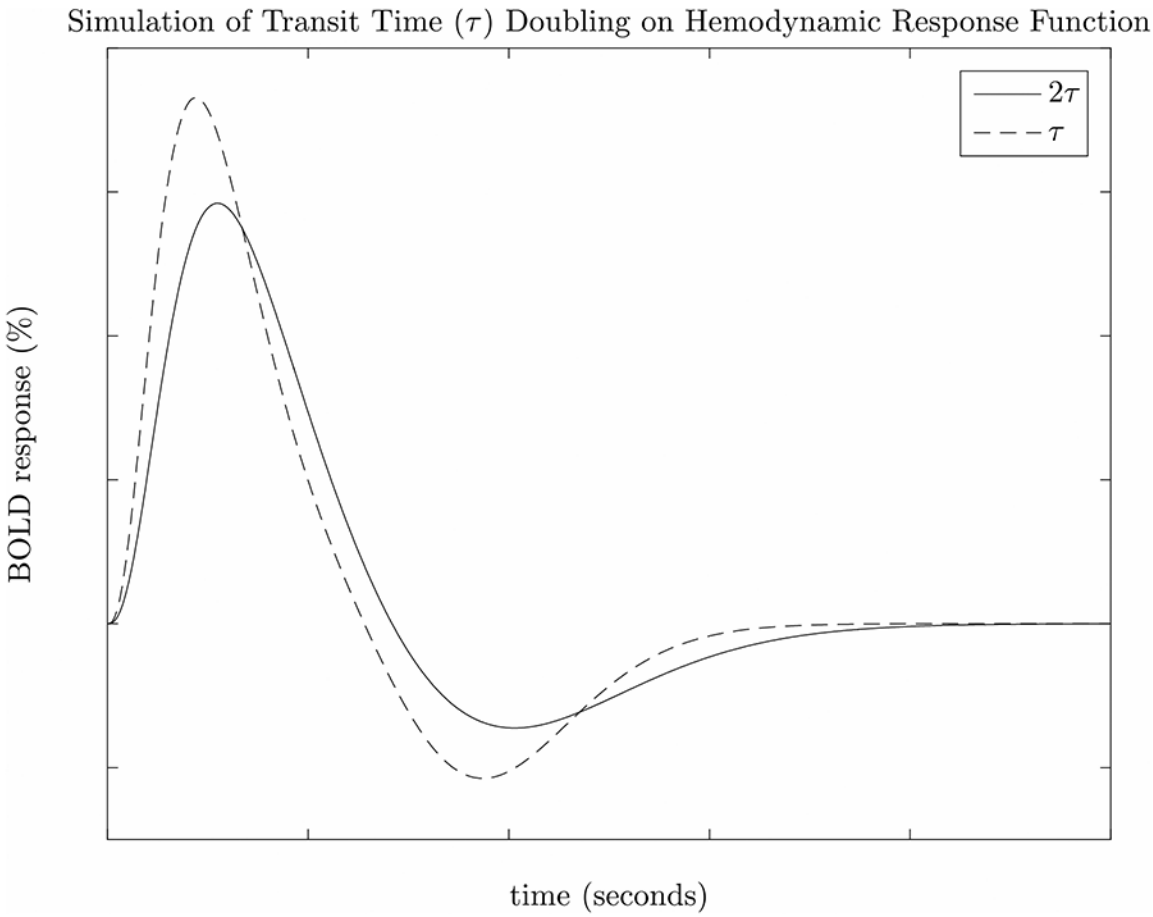


**Figure 1:**

The Hemodynamic Response Function is the regional Blood Oxygenation Level Dependent (BOLD) response generated from a brief peripheral stimulus, created through a sequence of vascular and metabolic dynamics. The transit time reflects the ratio of resting cerebral blood volume to resting cerebral blood flow. Doubling the transit time (solid line) attenuates both the overshoot and undershoot of the HRF, while also delaying the time to peak for the BOLD signal. Figure simulation adapted from (Friston, Mechelli et al. 2000).

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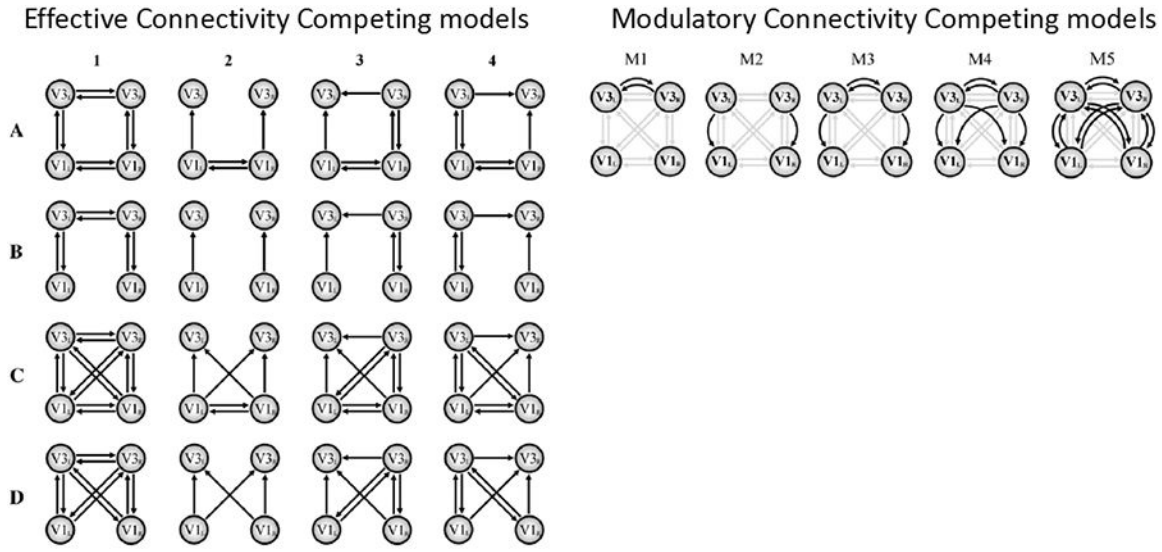


**Figure 2:**

Competing models of connectivity, compared using Bayesian model selection. We used dynamic causal modeling to model the regional coupling in the visual cortex in response to a checkerboard visual stimulus. Plausible models were nominated using neuro-anatomical and neuroimaging data following the previous work by Rytsar. Using Bayesian model selection, Model C1 was selected as the optimal architecture, while M5 was the best model of modulatory effects, replicating the earlier model-selection findings of Rytsar in a different dataset. Model A variants included bilateral connections between primary visual regions (V1), which were omitted in Model B. Model C variants all included bilateral cross-hemispheric connections between primary visual areas, but also contained both unilateral and bilateral cross connections between both regions and hemispheres (e.g. V1L→ V3R). Model D variants similarly investigated cross-connections between regions and hemispheres, but omitted the bilateral primary visual connections amongst V1 regions. Model 1 variants were exclusively bilateral connections, while Model 2 variants all lacked bilateral connectivity between higher-order (V3) visual areas. Model 3 families included connectivity from V3R to V3L, while Model 4 families included connectivity from V3L to V3R.

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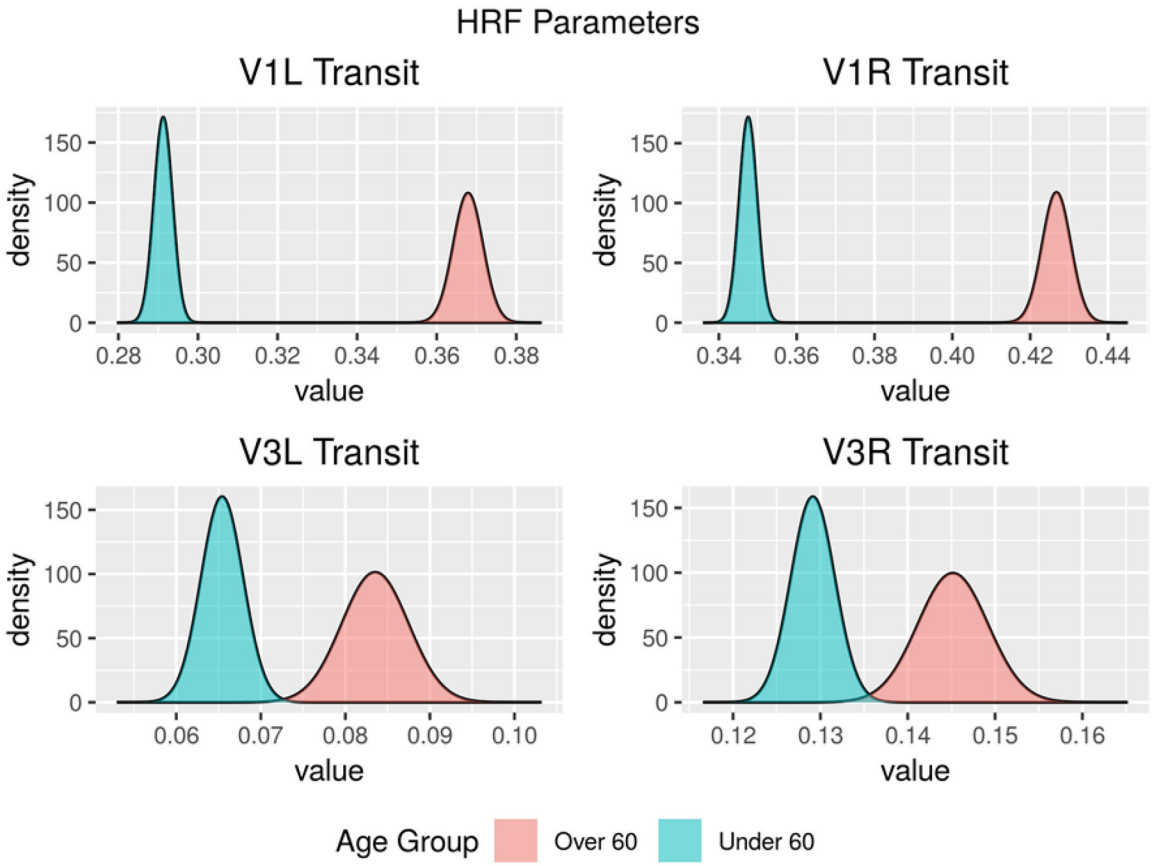


**Figure 3:**

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.

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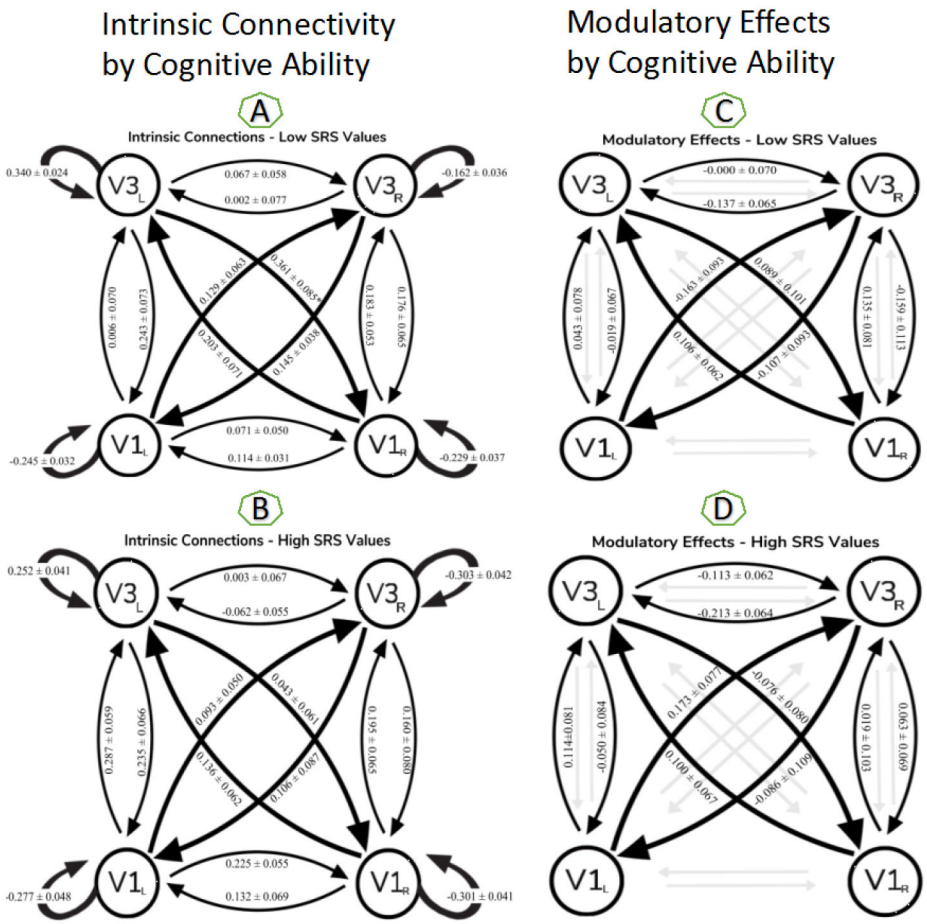


**Figure 4:**

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.

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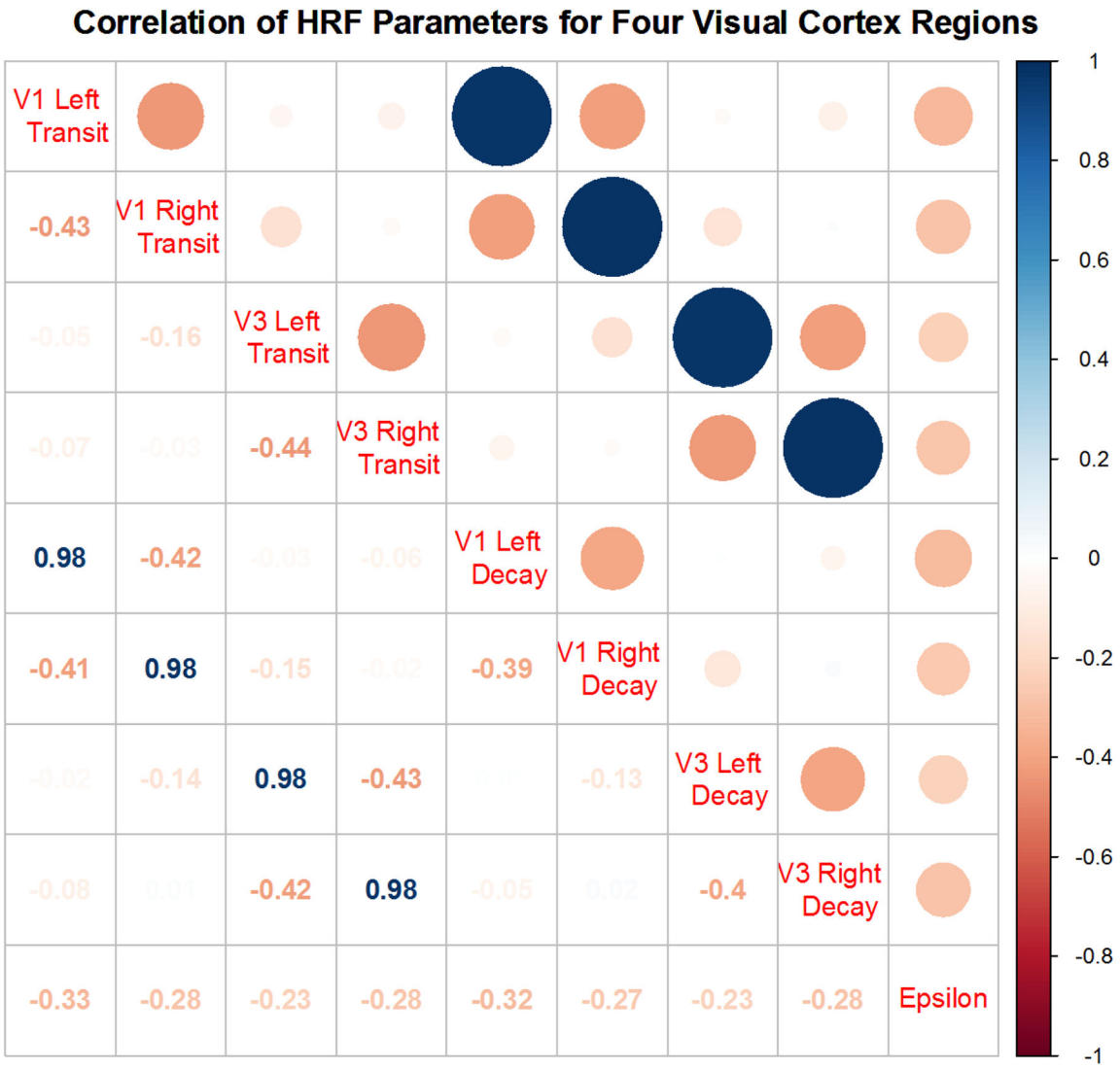


**Figure 5:**

Correlation of HRF parameters extracted within four regions of the visual cortex: Left and Right hemispheres for V1 and V3 regions. Because transit and decay have similar impact on the hemodynamic response function, these estimates were highly correlated within each region. Because these parameters are statistically redundant, only the transit parameter was selected for analyses.

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**Table 1:**

Increased transit time in the V3 left and right cortical regions was associated with reduced cognitive ability, independent of all other cerebrovascular and demographic covariates. Alcohol use was associated with reduced overall cognitive functioning (IQ 2.8 pts, $p<0.05$) while cardiac disorders (3.3 IQ pts; $p<0.05$), high cholesterol (3.9 pts; $p<0.05$), and years of education (2 IQ pts/year; $p<0.001$) were associated with higher general cognitive ability holding constant all else.

| Variable | Estimate | Std. Error | t-value | Pr(>\|t\|) | Significance |
|---|---|---|---|---|---|
| (Intercept) | 69.148 | 6.232 | 11.096 | 0.000 | *** |
| Age | 0.005 | 0.045 | 0.102 | 0.918 | |
| Male Sex | 2.165 | 1.263 | 1.714 | 0.087 | . |
| Years of Education | 1.930 | 0.318 | 6.065 | 0.000 | *** |
| Race: Other | 4.385 | 9.914 | 0.442 | 0.659 | |
| Race: White | 6.849 | 5.012 | 1.366 | 0.173 | |
| Socio-Economic Status | −0.002 | 0.105 | −0.023 | 0.981 | |
| Cardiac Diagnoses | 3.278 | 1.329 | 2.467 | 0.014 | * |
| Heavy Alcohol Use | −2.736 | 1.258 | −2.175 | 0.030 | * |
| High Cholesterol | 3.864 | 1.389 | 2.782 | 0.006 | ** |
| Hypertension | 0.227 | 1.548 | 0.147 | 0.883 | |
| Type 2 Diabetes | −2.989 | 2.719 | −1.099 | 0.272 | |
| BMI | −0.191 | 0.107 | −1.789 | 0.074 | . |
| Smoking | 0.849 | 1.602 | 0.530 | 0.596 | |
| Transit V1 Left | −3.725 | 5.070 | −0.735 | 0.463 | |
| Transit V1 Right | −3.890 | 5.009 | −0.776 | 0.438 | |
| Transit V3 Left | −11.274 | 5.573 | −2.023 | 0.044 | * |
| Transit V3 Right | −14.750 | 5.790 | −2.548 | 0.011 | * |
| Other: Socioeconomic Status | −0.146 | 0.265 | −0.549 | 0.583 | |
| White: Socioeconomic Status | 0.054 | 0.115 | 0.470 | 0.639 | |

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**Table 2:**

Both general cognitive ability (IQ) and specific cognitive domains were assessed. Our results suggest that increased hemodynamic latency in the V3 Left and V3 Right regions predicted reduced overall cognitive ability (WASI-II; IQ measurement). Specific domains were also found. See discussion for more information.

| Assessment | Raw Variables | Hemisphere | Significance |
|---|---|---|---|
| DKEFS- Tower | Total Achievement Score Total Rav | L | * |
| DKEFS- Letter Fluency | Letter Fluency Raw | | |
| DKEFS- Category Fluency | Category Fluency Raw | R | * |
| DKEFS- Category Switching Fluency | Category Switching Raw | | |
| DKEFS-Trails - Visual Scanning | Visual Scanning (Time) | | |
| DKEFS-Trails - Number Sequencing | Number Sequencing (Time) | | |
| DKEFS-Trails - Letter Sequencing | Letter Sequencing (Time) | L | * |
| DKEFS-Trails - Number-Letter Switching | Number-Letter Switching (Time) | | |
| DKEFS-Trails - Motor Speed | Motor Speed (Time) | L | * |
| RAVLT | Delay - Total Correct | R | * |
| WASI | full scale IQ composite score | L,R | *,* |
| WASI-II Vocabulary | Vocabulary Raw Score | | |
| WASI-II Block Design | Block Design Raw Score | | |
| WASI-II Matrix Reasoning | Matrix Reasoning Raw Score | | |
| WASI-II Similarities | Similarities Raw Score | L,R | **,* |