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Cognition and brain changes associated with high-dose atorvastatin: A BOLD proposition?

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HMG CoA reductase inhibitors have become a cornerstone of treatment for cardiovascular disease. ACP/AHA guidelines recommend initiation of statins for secondary prevention of coronary diseases in adults under age 75 and primary prevention in adults 40-75 with diabetes mellitus or an LDL above 70.¹ Additionally, most experts support the use of high doses of the medications to achieve LDL goals. As a result, nearly 40 million Americans take statins on a daily basis.² While the primary biological goal is lipid lowering, substantial evidence points to a broader set of mechanisms conferring benefits across an array of systems and disease processes.³ These pleiotropic effects include anti-inflammatory and antioxidant properties. With an increase in use, concerns about adverse effects, including cognitive impairment, have also risen. Despite publications of systematic reviews finding no difference in performance on cognitive measures between treated and untreated patients in randomized controlled trials,⁴ concerns about cognitive effects in the literature and lay press persist. Given wide heterogeneity in analytical models and cognitive measures in stain trials,⁵ Taylor et al aimed to corroborate changes in cognitive performance with fMRI in a trial of patients receiving high dose Atorvastatin. Given the prevalence of statin use and conflicting results with respect to cognitive function, the authors have chosen to address an issue with important health policy implications. Nonetheless, the methods chosen have partially obscured their ability to detect changes in neuronal activity in response to statin treatment, but conversely their results may further support statin-related pleiotropic action on neurovascular coupling.

At their core, functional magnetic resonance imaging (fMRI) analyses rely upon comparison of image signal intensity differences caused by changes in deoxygenated and oxygenated hemoglobin concentrations in response to neuronal activity. When neural activity occurs regional cellular energy consumption levels increase prompting a concomitant vascular hemodynamic response increasing blood flow to the region. The inflow of oxygenated hemoglobin to meet regional neuronal activity demands causes a shift in the ratio of oxygenated to deoxygenated hemoglobin. Deoxygenated hemoglobin is inherently paramagnetic while its oxygenated state is diamagnetic. Changes in the magnetic resonance signal between these two hemoglobin states is the basis for most fMRI studies and is termed Blood Oxygenation Level Dependent (BOLD) signal. In essence, BOLD signal is an endogenous contrast medium for inferring neuronal activation from regional microvascular changes characterized by a standard, canonical hemodynamic response function (HRF). While not a direct measure of neuronal activity per se, BOLD signal fMRI has been shown to be a reliable and robust functional neuroimaging technique to assess not only task-related brain activity but also whole brain functional networks (e.g., resting-state fMRI).

The BOLD signal HRF peak (i.e., maximal level of inflowing oxygenated hemoglobin) occurs approximately 6 seconds after regional neuronal activity initiation and can be used to infer neuronal

activation from a single stimulus event-type and is termed event-related fMRI, as was conducted by Taylor et al in their study of high-dose atorvastatin. Alternatively, the HRF peaks associated with a cognitive state can be averaged over a longer period and analyzed in what is termed block-design fMRI. Each BOLD fMRI technique has its advantages and potential pitfalls. Event-related fMRI designs have greater sensitivity to infer subtle or discrete neuronal activity in response to stimulus characteristics, but may be at greater risk of inferring neuronal activation from extraneous factors affecting the canonical HRF. Conversely, block-design fMRI studies at a cost of diminished discrete stimulus neuronal activity detection tend to be more robust and resistant to potentially confounding perturbations of the physiological components that contribute to BOLD signal.

Selection of BOLD fMRI analysis type should be guided by multiple factors, the most important of which should be considerations associated with systematic differences in cerebrovascular functioning that could significantly impact the HRF and thus the very basis upon which neuronal activity is inferred in BOLD fMRI. BOLD signal represents a complex interaction between cerebral blood volume and coupled cerebral blood flow and cerebral oxygen metabolic rate (CMRO₂). Any conditions or diseases (e.g., uncontrolled hypertension), physiological states (e.g., hypercapnia), substances or medications (e.g., benzodiazepines) that significantly alter these BOLD components on a macro- or microvascular level may meaningfully impact BOLD fMRI analyses. For these and other reasons, pharmacological trials examining for neuronal differences using BOLD fMRI techniques require additional scrutiny and careful interpretation.

The effects of statins on cerebral hemodynamics is an area of growing interest given competing clinical trial and observational studies of both beneficial pleiotropic effects in older individuals at risk for dementia and cognitive complaints in others.^{4,5} Giannopoulos et al.⁶ compile animal model and trial evidence that long-term statin use reduces stroke incidence and severity of outcomes through upregulation of endothelial nitric oxide synthase (eNOS). This, in turn, improves cerebrovascular vasomotor reactivity and cerebral blood flow through increased bioavailability of nitric oxide; two possible cholesterol-independent improvements that could reasonably impact BOLD signal characteristics. Trial evidence specific to high-dose atorvastatin (80 mg) suggests that vasomotor reactivity is improved in patients with controlled hypertension and hypercholesterolemia,⁷ and particularly pertinent to the current Taylor et al. study, a 4-month randomized, controlled, double-blind trial of low dose atorvastatin (40mg) in asymptomatic mid-life adults found that the statin was associated with significant and systematic alteration of HRF characteristics in an event-related fMRI analysis.⁸ Specifically, 4-month atorvastatin treatment relative to placebo resulted in quicker HRF response latency and higher HRF peak amplitudes in certain brain regions during a subsequent memory fMRI task paradigm, similar to one of the tasks used by Taylor et al. The atorvastatin-related effects on the HRF characteristics were observed independent of any significant differences between groups in cerebral blood flow or perfusion times. This lack of association with large vascular changes suggests that atorvastatin's effects on the HRF latency and peak amplitude characteristics may reflect atorvastatin's more basic influence on neurovascular coupling, possibly through eNOS upregulation. Alternatively, atorvastatin's lipophilicity, effects on blood-brain barrier permeability, and anti-inflammatory action may mean that there are other statin-associated direct neuronal effects that may be reflected in basic HRF component changes. In either case, one might posit that BOLD signal contrast may not be the best neuroimaging method for inferring statin-related neuronal activities differences. Without certain fMRI analytical controls this would reasonably be a correct assumption, but Taylor et al. in one of their event-

related fMRI tasks wisely include a temporal derivative function to the standard canonical HRF when making their group x time BOLD signal comparisons. A temporal derivative function allows one to capture differences in the latency of the HRF peak amplitude, and one could also include a dispersion derivative function to capture differences in the duration of the amplitude peak. Often these temporal basis functions are not included because they reduce the overall power of an event-related fMRI analysis, but the inclusion of these temporal and dispersion temporal basis functions are critical when there may be systematic changes to basic HRF characteristics between groups or treatments, such as those seen in the Xu et al.⁸ 4-month, low-dose atorvastatin trial.

Greater confidence for possible statin-related neuronal changes would be associated with event-related fMRI tasks and models that account for HRF component variability. Taylor et al. reasonably accounted for HRF variability between groups and over time on BOLD signal changes associated with the maintenance phase of a working memory task (i.e., a task phase is akin to maintaining a phone number in your mind for more immediate recall). In their event-related fMRI analysis of the working memory task data, a significant group x time interaction locus was detected in the right putamen/globus pallidus region. Those individuals treated with high-dose atorvastatin had reduced “temporally-corrected” BOLD signal HRF amplitudes relative to controls on placebo, but an inverse of this relationship after medication wash-out. While not statistically significant ($p=0.055$) there was a trend over time in the atorvastatin group for increased BOLD signal amplitudes from treatment to wash-out that was not observed in placebo controls. These subcortical BOLD changes during fMRI working memory task performance were independent of behavioral performances on the task, suggesting that treatment and placebo groups may have systematic differences in regional brain activity necessary to accomplish the working memory task at similar performance levels.

The same level of confidence for possible statin-related neuronal changes cannot be expressed for Taylor et al. figural memory event-related fMRI results. This is largely due to a lack of control for possible HRF component changes as seen by Xu et al,⁸ but also due to regional findings in midline parietal and bilateral paracentral lobule that are not consistent with known fMRI patterns associated with subsequent memory task paradigms (e.g., contrast of BOLD HRF peak amplitudes associated with brain activity during encoding of stimuli that are later remembered versus forgotten). It could be that the observed group x time interaction in the parietal region during this successful memory encoding task reflects statin-related influence on the HRF or on neuronal functioning, but a general lack of within-group change over time in the BOLD signal for both groups does not provide strong support for either possibility.

In summary, we do not question that importance of continued inquiry into the mechanisms and effects of statins on neurocognitive function. Given the likely use of statins over decades by tens of millions of Americans, it is imperative that we begin to meaningfully sort out the benefits and harms of these medications. The evidence presented by Taylor et al. does not end this debate, but rather starts a more focused conversation regarding disentangling pharmacological neuroimaging study results where the methods may reflect the interplay of peripheral pleiotropic effects and neuronal activity. There may be additional utility in BOLD fMRI to better understand the mechanisms of lipophilic statins on neurovascular function, but definitive statements about statin effects on neuronal activity patterns will likely require additional neuroimaging techniques, such as magnetoencephalography (MEG) or electroencephalography, or at the very least tight analytical control of variance in HRF characteristics

(e.g., block-design fMRI or event-related fMRI with temporal and dispersion derivatives) and the implementation of cross-over designs.

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