

# CASE REPORT

## Changes in Memory Function and Neuronal Activation Associated with Atorvastatin Therapy

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A small number of case studies have reported statin-induced dementia or memory loss that resolves with cessation of statin therapy. However, such reports have not, to our knowledge, been substantiated by objective measures of changes in brain function during statin treatment and after discontinuation of the drug. We describe a 65-year-old man who reported cognitive complaints (memory complaints and mood changes) after taking atorvastatin 10 mg/day for 1 year. He had no history of alcohol consumption, major head trauma, psychiatric problems, or memory impairment. Cognitive testing (Hopkins Verbal Learning Test–Revised, Brief Visuospatial Memory Test–Revised, and Wechsler Adult Intelligence Scale, third edition, digit symbol coding and digit span tests) and assessment of neuronal activation using functional magnetic resonance imaging (fMRI) were performed during a working memory task (Sternberg Task) while he was receiving atorvastatin therapy. The patient demonstrated altered neuronal activation (reduced activation of the dorso-lateral prefrontal cortex during the encoding task phase and hyperactivation of multiple areas of the prefrontal cortex during the recognition task phase) and reduced performance on the cognitive tests, which was consistent with his cognitive symptoms. These measurements were repeated 2 months after discontinuation of the drug. The patient exhibited improved cognitive test performance and fMRI patterns similar to those expected in a healthy individual. The patient also reported subjective improvement of his cognitive complaints within days of cessation of atorvastatin, which persisted at follow-up 5 months later (while refraining from any statin use in the interim). To our knowledge, this is the first case report to describe objective cognitive and fMRI findings substantiating statin-associated effects on the central nervous system, and it provides preliminary evidence that fMRI may be a useful technique for evaluating cognitive function in adults treated with statins.

**Key Words:** neuronal activation, magnetic resonance imaging, statins.  
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Patients occasionally complain of cognitive changes during statin therapy, and a small but growing number of case reports and studies have described statin-associated dementia and memory loss that resolve with cessation of statin therapy.<sup>1–5</sup> However, such reports have not, to our knowledge, been substantiated by objective measures of changes in brain function during and after discontinuation of statin treatment.

We describe changes in neuronal activation patterns, assessed by functional magnetic imaging (fMRI), in a patient who had cognitive complaints and concurrent changes in mental function during atorvastatin treatment.

### Case Report

A 65-year-old Caucasian man who had been taking atorvastatin 10 mg/day for 1 year as an

**Table 1. Results of Neuropsychological Testing**

Test	While Taking Atorvastatin	2 Months After Discontinuation of Atorvastatin
Hopkins Verbal Learning Test		
Total recall (trials 1–3)	23/–1.05/low average	24/–0.81/average
Delayed recall	6/–2.11/mildly impaired	9/–0.44/average
Retention	55%/–2.83/moderately impaired	90%/–0.08/average
Brief Visuospatial Memory Test		
Total recall (trials 1–3)	19/–0.5/average	19/–0.5/average
Delayed recall	8/–0.2/low average	9/0.3/average
Wechsler Adult Intelligence Scale		
Digit symbol coding	25/2.33/superior	26/2.66/superior
Digit span	72/1.33/very superior	80/1.66/very superior

Data are raw score/Z-score/rating based on Z-score.

outpatient at the institutional cholesterol clinic developed what he described as complaints of “fuzzy thinking” and “brain fog.” His wife also noted that the patient demonstrated a progressive decline in cognitive function and memory accompanied by increasing mood changes. The patient was otherwise well and had no history of alcohol consumption, major head trauma, psychiatric problems, or memory impairment. He provided written informed consent, approved by Hartford Hospital’s Institutional Review Board, to have further evaluation of his cognitive complaints performed.

The patient was evaluated with the Beck Depression Inventory<sup>6</sup> to exclude the possibility that his symptoms were a consequence of depression; he scored in the normal range. A series of three standard cognitive tests as well as an in-scanner fMRI–working memory task were administered during atorvastatin treatment. Cognitive tests included the Hopkins Verbal Learning Test–Revised (HVLTR),<sup>7</sup> which measures the encoding and recall aspects of declarative memory, the Brief Visuospatial Memory Test–Revised (BVMTR),<sup>8</sup> which assesses visual learning and memory, and the Wechsler Adult Intelligence Scale, third edition (WAIS-III), digit symbol coding and digit span

tests,<sup>9</sup> which assess processing speed and working memory, respectively. Alternate test versions of HVLTR (forms 1 and 6) and BVMTR (forms 1 and 2) were used before and after atorvastatin was discontinued to minimize learning effects. Based on Z-score measures, the patient’s scores ranged from impaired to superior on these cognitive tasks. A modified version of the Sternberg Task,<sup>10,11</sup> a test of working memory ability, was used to assess neuronal activation with brain fMRI acquired using a Siemens Allegra 3 Tesla scanner (Siemens AG, Munich, Germany). This task requires the subject to memorize a list of alphabetic consonants (encoding phase), maintain the list in memory during a delay interval (maintenance phase), and then be presented with “probe items” (response selection phase). Medium (4, 5, and 6 letters) and hard (6, 7, and 8 letters) versions of the task were used. Functional T2 weighted images were obtained using echo planar imaging sequence sensitive to blood oxygen level–dependent (BOLD) contrast. Before each scan, the patient was given comprehensive instructions and a 7-minute practice task implemented on a standard desktop computer equipped with custom presentation software. Alternate task versions were again administered in the on-drug versus off-drug conditions. Imaging data were analyzed using Statistical Parametric Mapping 2 software (Wellcome Institute, London, United Kingdom). Statistical analyses using a false-discovery rate threshold of a p value less than 0.05 were used to correct for multiple comparisons across the brain.

The patient reported subjective improvement of cognitive complaints within days of cessation of atorvastatin. After a statin washout period of 2

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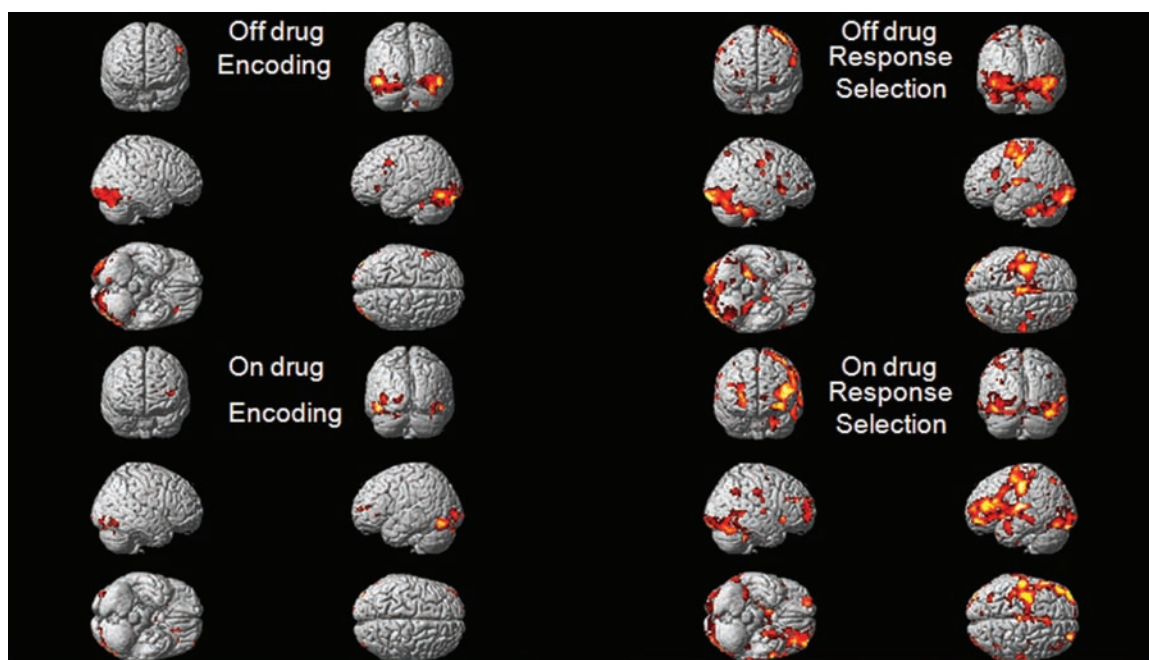
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months, evidence of significant improvement in cognitive function was noted (Table 1). His fMRI imaging also demonstrated changes in cerebral function during performance of the Sternberg task. Neuronal activation was comparable during the encoding phase of the medium-difficulty Sternberg task in the patient before and after stopping atorvastatin, although during the “off-drug” condition, the patient activated his dorso-lateral prefrontal cortex (DLPFC) more specifically. Moreover, during response selection, the patient tended to hyperactivate multiple regions in the prefrontal cortex (PFC) while taking the statin compared with after discontinuation of the statin. During the more difficult version of the Sternberg task (Figure 1), the patient showed almost no activation during the encoding stage of the task while taking atorvastatin. In contrast, after drug discontinuation, the patient robustly activated parts of DLPFC during encoding. The pattern of activation during response selection was similar to the medium condition, in which the patient tended to overactivate multiple PFC regions while taking drug, perhaps trying to overcompensate during the recognition stage for impaired encoding. Behavioral scores from the Sternberg task unfortunately could not be calculated due to corruption of data files in electronic storage.

During a follow-up visit approximately 5 months after completion of the second fMRI scan (while refraining from any statin use in the interim), the patient reported continued improved cognitive function consistent with that observed immediately after stopping the atorvastatin.

## Discussion

These preliminary data suggest that our patient demonstrated altered neuronal activation while taking atorvastatin, consistent with his reported cognitive symptoms and reduced performance on established cognitive tests assessing memory and learning. Of importance, these symptoms appeared to resolve with cessation of statin therapy, and the patient reported subjective resolution of his cognitive adverse effects, demonstrated improved cognitive test performance, and showed fMRI patterns similar to those expected in a healthy individual.<sup>11</sup> As the patient reported continued improvement in cognitive function 5 months after completion of the second fMRI scan, it is not likely that this individual suffers from overt cognitive impairment or dementia causing unusual fluctuations in cognition that would artifact changes observed during and after discontinuation of statin therapy. This premise is further supported by the fact that even while



**Figure 1.** Neuronal activation observed during the difficult version of the Sternberg Task, depicted by colored regions on the three-dimensional-rendered brains, during encoding (left panels) and response selection (right panels) while the patient was taking atorvastatin 10 mg/day (bottom panels) and 2 months after atorvastatin was discontinued (top panels).

taking statin therapy, the patient's scores on WAIS-III measures exceeded known thresholds for dementia or mild cognitive impairment.<sup>12,13</sup>

This report provides both neuropsychological testing decrements and what is, to our knowledge, the first fMRI-based evidence of changes in BOLD response during statin treatment in a patient complaining of statin intolerance. Specifically, the patient demonstrated reduced activation in the DLPFC and hyperactivation in the PFC during encoding and response selection phases, respectively, of the Sternberg task, with the observed on-drug versus off-drug changes greater in the difficult than in the medium Sternberg task conditions. The DLPFC is responsible for motor planning, organization, and regulation of intellectual function and action, and plays a role in working memory and sensory integration. The PFC underlies cognitive processes that constitute executive function. Of interest, activation in the DLPFC during attention, memory, and cognitive control functions is lower in certain disease conditions, such as schizophrenia<sup>14,15</sup> and major depressive disorder,<sup>16</sup> and recent evidence suggests that activation in the DLPFC during an inductive-reasoning task is also reduced in adults with mild cognitive impairment relative to age-matched controls.<sup>17</sup> In addition, hyperactivation of the medial PFC has been observed in schizophrenics and is thought to contribute to the disturbed thought patterns associated with the disease.<sup>15,18</sup> The combined pattern of reduced frontotemporal activation during encoding and hyperactivation during recognition phases of a verbal memory task is also exhibited by schizophrenic patients, and may underlie impaired cognitive scores on verbal memory tasks.<sup>19,20</sup> Thus, the collective data regarding altered neuronal activation in the DLPFC and PFC in patient populations suggest that these areas are affected by certain pathologies, producing observable cognitive deficits such as those exhibited by our patient; the DLPFC and PFC are also influenced by pharmaceutical interventions such as dopamine antagonism,<sup>21</sup> as well as donepezil and rivastigmine administration,<sup>22,23</sup> and may ultimately prove susceptible to statin therapy as well.

It should be noted that interpretation of fMRI data in a single individual has significant limitations: test-retest reproducibility of data is unknown, data are four dimensional and involve multiple comparisons of tens of thousands of voxel values varying in time (although statistical

analyses were corrected for multiple comparisons), and high-resolution measurements include noise and redundancy due to correlations within the data set.<sup>24</sup> Therefore, these findings should be confirmed with larger numbers of subjects who report cognitive complaints with an established causal relationship to statins.<sup>6</sup> Furthermore, additional studies are needed to determine if similar fMRI changes occur in asymptomatic patients treated with statins and to determine the clinical sequelae of any cerebral function changes that statins may produce. Nevertheless, given that reported cognitive effects of statins vary greatly among patients, and more objective studies of cognitive complaints are inconclusive,<sup>25-29</sup> fMRI studies may serve as a technique to evaluate the underlying basis of cognitive changes in patients during statin treatment.

## Conclusion

This case report describes an otherwise-healthy patient who complained of changes in mood and cognition while being treated with low-dose atorvastatin. Cognitive testing and fMRI imaging revealed decrements in cognitive function as well as altered neuronal activation associated with statin treatment. Further research using cognitive testing and fMRI imaging are necessary to confirm a small but growing number of reports suggesting that statins evoke adverse cognitive effects in certain individuals.

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