The Effect of High-Dose Atorvastatin on Neural Activity and Cognitive Function

Beth A. Taylor, Ph.D.
Director, Exercise Physiology Research, Department of Cardiology, Hartford Hospital
Associate Professor, Department of Kinesiology, University of Connecticut
Background

- Mild CNS complaints second most commonly reported adverse effect of statin drugs
  - 2012 FDA safety label change
- Study findings inconclusive
  - Observational studies prone to prescription bias
  - Traditional cognitive tests yield small effect sizes
Purpose

- To assess the effect of statins on cognition in a randomized clinical trial
- Battery of standard neuropsychological assessments
- Cognitive Failures Questionnaire (CFQ)
- Neural activation with functional magnetic resonance imaging (fMRI) during two tasks
  - Visual Figural Memory task and a verbal Sternberg Working Memory task.

Broadbent et al. 1982; Beason-Held et al. 2005; Sternberg et al. 1966
Study Design

• Participants aged ≥ 20 yr recruited from an ongoing RCT
• **Effect of Statins On Skeletal Muscle Performance (STOMP); NCT00609063**
• Designed to assess the incidence of muscle side-effects in 420 healthy, statin-naïve adults treated with 80 mg atorvastatin or placebo daily for 6 months
• **Study Design (B → A Order)**
  • Cognitive testing after 6 months on treatment
    – Paper-based neuropsychological tests and functional magnetic resonance imaging (fMRI)
  • Tests repeated after the participants ceased treatment for two months
• Blood lipids measured at both timepoints

Thompson et al. 2010; Parker et al. 2013
Neuropsychological Measurements

- Hopkins Verbal Learning Test-Revised (HVLT-R; auditory memory)
- Brief Visuospatial Memory Test-Revised (BVMT-R; visual memory)
- Symbol Digit Modalities Test (SDMT; general cognitive function and neurological impairment)
- Lafayette Grooved Pegboard (manual dexterity)
- Stroop Color-Word and Trail-Making Tests (attention, reasoning and executive functioning)
- Wechsler Adult Intelligence Scale III: Total and Reliable Digit Span (working memory)
- 18-point Clock Test (mild cognitive impairment)
- Cognitive Failures Questionnaire (CFQ; self-reported failures in perception, memory, and motor function)
Functional MRI Tests

• **The Figural Memory task:** visual encoding and recognition paradigm that consistently activates medial temporal, cingulate, inferior frontal, and posterior parietal brain regions
  – Encoding: memorization of black abstract line drawings
  – Recognition: Recognition of 20 target and 20 similar-appearing distractor stimuli

• **The Verbal Working Memory task:** reliable activation of dorsolateral prefrontal, anterior cingulate, posterior parietal, and subcortical brain regions
  – Encoding: Memorization of 2, 4 and 6 sets of consonants
  – Maintenance: 12 seconds of rest
  – Retrieval Phase: 18 trials with half target and half distractor

• Blood oxygen level dependent (BOLD) response modeled for behavioral events, covarying for motion and linear trends, controlling for age and sex

Cox et al. 2016; Dager et al. 2014; Meda et al. 2008
### Participant Characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Atorvastatin (n=66)</th>
<th>Placebo (n=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (n)</td>
<td>39</td>
<td>36</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.8 (14.7)</td>
<td>48.8 (14.7)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>15.2 (3.5)</td>
<td>16.2 (2.0)</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>120.4 (12.9)</td>
<td>120.0 (13.7)</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>77.2 (9.3)</td>
<td>75.6 (8.9)</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>27.1 (5.2)</td>
<td>27.2 (4.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>On-Treatment Lipids</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total-C (mg/dL)</td>
<td>128.3 (29.0)</td>
<td>195.6 (37.8)*</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>54.9 (21.3)</td>
<td>115.2 (35.7)*</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>55.6 (18.6)</td>
<td>58.1 (16.1)</td>
</tr>
<tr>
<td>TRIG (mg/dL)</td>
<td>82.7 (35.5)</td>
<td>101.0 (42.3)*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Off-Treatment Lipids</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total-C (mg/dL)</td>
<td>193.3 (34.8)</td>
<td>191.0 (35.2)</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>114.6 (31.7)</td>
<td>111.9 (29.8)</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>58.2 (16.3)</td>
<td>59.4 (15.0)</td>
</tr>
<tr>
<td>TRIG (mg/dL)</td>
<td>102.4 (52.1)</td>
<td>95.9 (43.9)</td>
</tr>
</tbody>
</table>

Data expressed as mean (SD). * indicates significant difference between atorvastatin and placebo groups at p < 0.01. C = cholesterol; LDL = low-density lipoprotein; HDL = high-density lipoprotein; TRIG = triglycerides.
Neuropsychological Test Scores

- Minimal effects
- Both groups: HVLT-R scores for total and delayed recall improved with drug cessation (p=0.01 and 0.04)
- Placebo group: Stroop Color-Word score increased (p<0.01) and 18-Point Clock Test score decreased (p=0.02) with drug cessation
- No difference in CFQ scores (all p > 0.10) by total score, frequency of score or domain (memory, distractibility, blunders, and names)
Figural Memory Task

- Participants were excluded from fMRI analysis if they did not have complete scans at both timepoints due to significant motion artifact, invalid behavioral responses, or inability to complete in-scanner testing.
- Sample size of 77 participants (42 placebo, 35 atorvastatin).
- **Group x time interaction in bilateral paracentral lobule/precuneus during the encoding phase**
- Participants on atorvastatin had more BOLD response than participants on placebo while on treatment ($F(1,73) = 8.06, p=.006$), but less BOLD response than patients in the placebo group after the treatment washout period ($F(1,73) = 11.82, p=.001$).
- Neither group showed a significant change in BOLD response between scans (Atorvastatin: $F(1,32) = 0.11, p=.747$, Placebo: $F(1,39) = 0.05, p=.826$).
- No group x time effects on neural response during recognition hits or on any behavioral data from the task (all $p >0.68$).
Neural Activation During Figural Memory Task: Group-Time Interaction
Sternberg Task

- Sample size of 120 participants (68 on placebo, 52 on atorvastatin)
- **Group x time interaction in the right putamen extending into the right globus pallidus during the maintenance phase**
- Participants on atorvastatin had less BOLD response compared to participants on placebo while on treatment \((F(1,116) = 8.30, p=.005)\), but after the treatment washout, participants in the atorvastatin group had more BOLD response than participants in the placebo group \((F(1,116) = 12.84, p<.001)\).
- The atorvastatin group also showed a trend toward an increase in BOLD response between scans \((F(1,49) = 3.78, p=.055)\), whereas the placebo group showed no change in BOLD response over time \((F(1,65) = 0.95, p=.33)\).
- There were no group x time effects during the encoding phase or the retrieval phase, no parametric effects of increasing memory load during any phase, and no group x time effects on any behavioral data from the task (all \(p >0.16\)).
Neural Activation During Verbal Working Memory Task: Group-Time interaction
Discussion

- Few changes standardized neuropsychological tests, a finding similar to those from large clinical trials
  - Meta-analysis of 14 studies with 27,643 participants
- Case reports of memory decrements with statin therapy continue to be published
- Patients report cognitive side effects as a leading cause of statin intolerance
  - Nocebo effect?
  - Methodological issues (small effect sizes, learning/practice effects)

Ott et al. 2015; Suraweera et al. 2016; Lakey et al. 2016
Discussion and Conclusions

- Study is the first to investigate the effects of statins on the CNS with fMRI
- **No convincing evidence of measurable verbal or nonverbal memory dysfunction due to statin medications**
  - Most regional networks activated similarly by both groups
- Participants on atorvastatin demonstrated small but significant altered patterns of regional neural activation on vs. off statin compared to participants treated with placebo
  - Treatment groups differed at both timepoints
- Clinical implications of these findings are unclear and warrant additional clinical trials
  - Occasional reports of memory loss and confusion?
Acknowledgements

• Hartford Hospital: Paul D. Thompson, C. Michael White, Gregory Panza, Amanda Zaleski, Donna M. Polk
• Olin MRI: Godfrey Pearlson, Alecia Dager, Shashwath Meda, Gregory Book
• Data Safety Monitoring Board: JoAnne Foody, Pamela Hartigan, and Ira Ockene
• The STOMP parent study: National Heart, Lung, and Blood Institute/National Institutes of Health grant RO1 HL081893 (Dr. Thompson)
• The STOMP ancillary cognitive study: National Heart, Lung, and Blood Institute/National Institutes of Health grant NHLBI 1R01HL098085 (Drs. Taylor and Polk)