

LEVETIRACETAM AND MEMORY FUNCTION

STUDY COMPLETED!

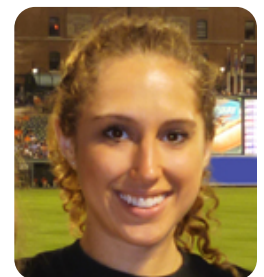
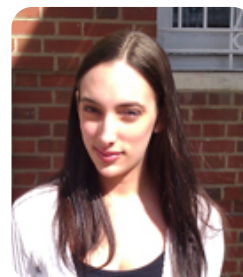
Greetings from the Levetiracetam and Memory Function study team. We are very excited to be able to share with you that we have completed enrollment and data collection for the levetiracetam and memory study! It has been a wonderful two and a half year experience, during which we saw over 140 people for screening visits and enrolled 88 individuals for participation in the study- some of whom participated in two phases of the study. In addition, I had the privilege of speaking to countless more people over the phone. We could not have completed this research without you, and I have been honored to share some of your time with you.

We are also very pleased to let you know that findings from this study were published this past May in a prestigious scientific journal. The report contains findings from individuals who participated in the study between January 2010 and January 2011, and again, we could not be more grateful for your help. I am sure many of you who had a MRI with us have not forgotten the experience; it is likely the most taxing activity in the study, but those MRI sessions produced stunning results! Functional magnetic resonance imaging, or fMRI, allowed previous studies to show that people with mild memory problems had different levels of activity in one of the areas of the brain used for forming memories, called the hippocampus. Results from the first phase of our study showed that when those participants were taking levetiracetam, that activity was essentially normalized.

In addition, participants on the medication improved their performance on the picture memory task that you performed in the scanner. These findings are truly exciting and very promising! Please find a copy of alzforum.org's report about our study on the following page.

FAREWELLS

We would like to extend our appreciation and farewells to Alica Diehl, our coordinating assistant, who worked with many of you throughout the study, and Lauren Jones, who was responsible for the MRI sessions and a lot of our data analysis. Alica has begun a teaching position with healthcorps, working to bring better health to Baltimore city youth and Lauren is moving to Dallas to be closer to her family and pursue a career in database management. Our work could not have progressed at the same pace without them, and for that we are grateful. Good luck Lauren and Alica!



Epilepsy Drug Calms the Hippocampus, Aids Memory

By Gwyneth Dickey Zakaib, alzforum.org

9 May 2012. Research suggests that the hippocampus goes into overdrive in people who may be on the path to Alzheimer's disease (AD). Is the excess neural activity helping these folks to remember, or making them forget? A study in today's *Neuron* by Michela Gallagher, Johns Hopkins University, Baltimore, Maryland, suggests the latter. When treated for two weeks with a low dose of an activity-dampening anticonvulsant drug, patients with amnesic mild cognitive impairment (aMCI) showed reduced hippocampal activity and performed better on a memory task. Though preliminary, the results suggest that suppressing hippocampal hyperactivity could be a therapeutic approach for early AD.

"Many of us have long suspected that hippocampal hyperactivation is a harmful response in patients with mild cognitive impairment," said Brad Dickerson, Massachusetts General Hospital, Charlestown. "This is the first time anyone has really tested that hypothesis and provided compelling data that this is a target for treatment."

In humans, greater hippocampal activation was observed in people with aMCI (see Dickerson et al., 2005), asymptomatic ApoE4 carriers (see ARF related news story), and people carrying familial AD mutations (see Quiroz et al., 2010). Some researchers believed that, hampered by AD pathology, the hippocampus was recruiting additional, compensatory resources (see Dickerson et al., 2004, and Hämäläinen et al., 2007). More recent research suggested that the hyperactivation could result from a loss of hippocampus inhibitory function (see Andrews-Zwilling et al., 2010) and may be closely tied to neurodegeneration (see ARF related news story). Anti-epileptic drugs, including levetiracetam, dialed back hippocampal hyperactivity in aged, male Long-Evans rats—which also show a boost in hippocampus action and memory impairments (see Wilson et al., 2006). The drugs improved the rats' spatial memory performance (see Koh et al., 2010). Would a similar reduction in humans help as well?

First author Arnold Bakker and colleagues tested this idea in 17 people diagnosed with aMCI and 17 age-matched healthy controls over two, two-week treatment phases. All controls received placebo for both phases, while patients received levetiracetam in one phase and placebo in the other. The two phases straddled a four-week washout period. Levetiracetam is FDA approved for epilepsy patients. It quiets firing in neurons with both normally and abnormally elevated firing rates, especially in neurons that fire in bursts.

At the end of each treatment phase, the researchers performed high-resolution functional magnetic resonance imaging (fMRI) scans while participants completed a memory task that calls on the dentate gyrus (DG)/CA3 region of the hippocampus. The task was to view a series of images of everyday objects and indicate whether they were "old" (had been shown before), "new" (had not), or whether they were "similar" to one that had already been viewed. The researchers paid special attention to the "similar" items, because mistaking one for an "old" item meant that the memory of a previously viewed object interfered with a new representation of a look-alike. Participants also underwent a series of neuropsychological tests after each treatment phase.

During the "similar" series, aMCI patients on placebo treatment had more activation in the DG/CA3 region than did their age-matched counterparts. They also made more errors, judging more similar items as "old." The researchers hypothesized that if the hippocampal hyperactivity was helpful, then decreasing its function should worsen memory in aMCI patients. Instead, two weeks on a low dose of levetiracetam (less than half of that given to epilepsy patients) improved task performance. Treated patients made fewer memory errors judging similar items. Patients on the drug also activated their hippocampus less during the memory task, suggesting that the hyperactivation hindered performance in the first place. "It was unclear whether hyperactivity was a beneficial compensatory response or just a detrimental

Epilepsy Drug Calms the Hippocampus, Aids Memory, cont.

overactivation of neuronal networks," said Jorge Palop, University of California, San Francisco. "The data clearly suggest ... a primary and detrimental effect of network hyperactivity in MCI patients."

While performance on the other neuropsychological tests did not differ between placebo and drug patients, it is likely that assessments after a longer period of drug treatment would be needed to observe whether there were any drug-induced improvements in global memory, Gallagher said. Nevertheless, "these data provide evidence that perhaps treating hyperactivity could be a benefit to people with aMCI," she said.

This finding could be but one small piece of a larger puzzle, said Gunnar Gouras, Lund University, Sweden. While some areas of the brain could be hyperactive and need calming down, others could be hypoactive and require a boost, he pointed out. "If we only consider hyperactivity, we're oversimplifying." A fuller understanding of the affected circuits is probably needed in order to affect global memory, he said.

For instance, Gallagher and colleagues previously showed that the entorhinal cortex, which is hit earlier and harder in AD, was hypoactive in patients with MCI performing a pattern separation task (see Yassa et al., 2010). "If you're really going to try to make a strong impact on Alzheimer's disease, one would imagine that drugs that benefit the entorhinal cortex should be developed as well," said Scott Small, Columbia University in New York.

As for immediate implications for treatment, all researchers interviewed for this article agreed that formal clinical trials of levetiracetam's long-term safety profile and effectiveness will be needed in aMCI patients before doctors should consider prescribing it to them.

"I think it would be premature for any physician to be prescribing it off-label," said Jessica Langbaum, Banner Alzheimer's Institute, Phoenix, Arizona, who is helping design and execute upcoming presymptomatic Alzheimer's treatment trials. This is just one short-term study with a small sample size that has not yet been replicated, Langbaum pointed out. To find out whether there is a true clinical benefit, the drug needs to be tested on more patients for a longer period of time, she said. The Food and Drug Administration declined comment on its procedures for clinical trials in a case like this.

A separate, one-year study of levetiracetam in AD patients who had seizures suggested that the drug does improve attention level and oral fluency, and is safe for use in controlling seizures in AD patients (see Cumbo and Ligor, 2010). However, Gallagher added that those benefits could have resulted from reduced seizures rather than global cognitive benefits. What's more, the patients had AD rather than MCI, so by that point their hippocampal activity was likely reduced relative to controls. Therefore, studies on the drug's effectiveness at the MCI/prodromal stage of AD are needed, she said.

Gallagher plans on conducting clinical trials in the near future. She is currently testing different doses in the same experimental paradigm. "We want to be very careful to understand what exposure to this drug might do, particularly in this vulnerable population," Gallagher said. "There is a possibility that overactivity itself is bad for the brain, and controlling it could have some long-term benefit, but we don't know that."

In related findings, Palop and colleagues recently reported that genetically reducing abnormal cortical firing by way of boosting inhibitory neurons improved memory in a familial mouse model of AD (see ARF related news story). Both sets of data point to the potential future utility of reducing neural activity in the treatment of very early AD.—Gwyneth Dickey Zakaib.

CURRENT AND FUTURE WORK

We have now completed data collection on two additional doses of the medication. Our last participant completed participation on July 20th of this year, and we are analyzing the collected data in hopes of identifying an ideal dose for future studies for mild cognitive impairment. We have been greatly encouraged by our initial findings and we are working as hard as we can to determine whether this medication will be helpful as a long-term therapy for people suffering from memory loss. Our next important step is to conduct a study that involves taking this medication for an extended period of time, and we are working hard to obtain funding to be able to start such a study. I hope those of you who worked with us in the past might consider participating with us again in the future!

Thank you again from the Levetiracetam Study Team!



Michela Gallagher, Ph.D.
Professor, Psychology & Neuroscience



Gregory Krauss, M.D.
Professor, Neurology



Arnold Bakker, Ph.D.
Asst. Professor, Psychiatry & Behavioral Sciences



Caroline Speck, B.A.
Sr. Research Program Coordinator

WHY LEVETIRACETAM?

Levetiracetam is used to treat epilepsy by decreasing abnormal activity in the brain, specifically the hippocampus. The hippocampus plays a crucial role in forming memories, and it is also where people with mild cognitive impairment, or MCI, express abnormal activity (though at much lower levels). In animal models, tiny doses of levetiracetam have lowered the activity levels and improved memory! This animal research has formed the foundation for our current studies in humans.

QUESTIONS?

Please contact:

Caroline Speck, B.A.
Sr. Research Program
Coordinator

Phipps Bldg 345
600 N Wolfe Street
Baltimore, MD 21287
cspeck1@jhmi.edu

410.955.5057 (office)
410.955.3108 (fax)