

## Woodrow Wilson Undergraduate Research Fellowship Proposal

**Introduction**

Schizophrenia is a debilitating psychiatric disorder that affects 1 in 200 individuals in the population, with peak incidence between the ages of 15 and 24 years (Messias et al., 2007). Clinically, the disorder is most prominently characterized by psychosis, including hallucinations, delusions, and paranoia. These symptoms are thought to originate from neurochemical imbalance such as excessive dopamine receptor activation in the mesolimbic pathway, which is the primary target of existing antipsychotic medications prescribed for the treatment of schizophrenia. Cognitive deficits including impaired memory function and executive controls are increasingly recognized as key features of schizophrenia, but are not effectively treated by available antipsychotics. Because untreated features of schizophrenia, especially impaired cognition, predict long-term disability and poor patient outcomes (Green et al., 2004), it is critical to develop effective therapies for the spectrum of this illness.

Recent observations, drawn from animal models and human neuroimaging studies, indicate that altered neural activity in the hippocampus, a brain area critical for memory formation, may contribute to cognitive impairment. Specifically, evidence suggests that hippocampal dysfunction observed in schizophrenia patients, as well as in animal models of schizophrenia, may be due to aberrant excess neural activity in the hippocampus (Lodge & Grace, 2011; Schobel et al., 2009, Schobel et al., 2013). Treatment with pharmacological compounds that boosts inhibition in the central nervous system would thus be expected to normalize the excess activity in the hippocampus and improve hippocampal-dependent memory function. In addition, targeting hippocampal overactivity may reduce excess dopamine activation because the hippocampal neurons and the dopaminergic neurons in the ventral tegmental area are functionally connected, potentially alleviating the psychotic symptoms of schizophrenia associated with dopamine dysregulation.

A series of recent groundbreaking work from the laboratory of Dr. Michela Gallagher, a Krieger-Eisenhower Professor of Psychology and Neuroscience at Johns Hopkins University, showed that treatment with pharmacological agents aimed at targeting hippocampal hyperactivation in another disorder provided remarkable improvement in cognition. Using a well-established animal model of neurocognitive aging, Dr. Gallagher and colleagues showed that cognitively-impaired aged rats with neuronal hyperactivity in the hippocampus benefited cognitively from treatment with drugs that boost inhibition such as antiepileptic agents (levetiracetam and valproate) and GABA agonists (Koh et al., 2010, 2013). Importantly, that novel treatment strategy to improve age-related memory impairment has now been translated to the clinic. Individuals with mild cognitive impairment (MCI), a precursor stage to Alzheimer's disease, showed a similar localization of excess neural activity in the hippocampus, which is thought to contribute to the cognitive impairment. Chronic treatment with the antiepileptic agent, levetiracetam, in this patient population effectively reduced hippocampal hyperactivation as shown by functional magnetic resonance imaging and improved hippocampal-dependent memory performance (Bakker et al., 2012).

Based on these remarkable findings, I propose using the same rationale and approach to treat cognitive impairment associated with schizophrenia. Under the supervision and mentorship of Dr. Gallagher, I will use two animal models of schizophrenia to assess the effectiveness of levetiracetam to normalize hippocampal hyperactivity and to improve memory function. The data from the proposed projects could open new avenues for therapeutics treatments of schizophrenia. Additional preclinical studies could expand on the role of levetiracetam used in this preliminary research to confirm the mechanism of action. Furthermore, if treatment with levetiracetam provides cognitive benefit in the preclinical models of schizophrenia, this well-tolerated drug could be tested in patients with schizophrenia to assess target engagement and effects on cognition. Hence, my proposed studies here could potentially provide a translational platform for bridging between the animal studies and clinical proof-of-concept using an FDA-approved therapeutic as well as supporting further research into a novel pharmacology to treat cognitive impairment in schizophrenia.

**Project Design**

As a preclinical proof of concept, I propose testing the efficacy of the antiepileptic agent, levetiracetam, to improve memory performance using a rat neurodevelopmental model and a rat psychomimetic drug stimulation model of schizophrenia. The neurodevelopmental model uses an antimetabolic agent to disrupt the proliferation and migration of neuronal precursor cells during gestation. As young adults, rats treated prenatally with the antimetabolic agent have significantly higher in vivo and in vitro hippocampal firing rates compared to

vehicle-treated controls (Gill et al, 2011; Sanderson et al., 2012) and showed hippocampal-dependent memory deficits (e.g., Gourevitch et al., 2004). The drug stimulation model uses the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine to generate psychosis. Animals treated chronically with ketamine showed in vivo hypermetabolism in the hippocampus and impaired cognition, consistent with that observed in schizophrenia patients (Gastambide et al., 2013; Schobel et al., 2013). To assess the efficacy of levetiracetam treatment to rescue cognition in these rat models, a radial arm maze task will be used. The task allows for the assessment of spatial memory, which is known to be dependent on the functional integrity of the hippocampus, and also allows for within-subject assessment of different drug doses to locate an optimal dose.

In light of the finding that hippocampal output via the subiculum control dopamine neuron firings in the ventral tegmental area (Floresco et al., 2001), I further hypothesize that treatment with levetiracetam aimed at reducing hippocampal hyperactivity would normalize dopamine dysregulation. Using the same animal models described above, rats will be tested for amphetamine-induced locomotor response in an open field test. Amphetamine is a drug that releases dopamine and causes paranoia, hallucinations, and increased locomotor behavior. The blockage of an amphetamine-induced increase in locomotor response in animals has been widely used as a behavioral assay for antipsychotics (Lipska & Weinberger, 2000). In the present case, levetiracetam is expected to reduce the increase locomotor activity induced by amphetamine similar to the effect of antipsychotic treatment, but via different mechanism of action.

### Academic and Scientific Training Background

I have long been interested in the neural basis of memory dysfunction. Last summer, I was accepted to the Science Scholars Program at Tulane University in my hometown of New Orleans, which introduced me to behavioral and neuroscience research. This program emphasizes the development of essential laboratory skills, including animal testing and benchwork, as well as the understanding of the latest research findings, including those on memory disorders. Since then, I have greatly expanded the breadth of my neuroscience knowledge through college coursework; in particular, the Cognitive Neuroscience curriculum has exposed me to the human memory systems and the different methods used to investigate memory localization and function, from neuroimaging to neurochemical lesions.

This semester, I further developed my research skills by training rigorously in Dr. Michela Gallagher's laboratory in the Department of Psychological and Brain Sciences. I have learned animal surgery, blood sampling, and brain harvesting. Importantly, I have, with a fair amount of independence, trained and tested rats on a maze to assess memory function. The preliminary data I have collected were useful in refining the design of the project I outlined here. Dr. Gallagher's lab, with the appropriate facility and support, would be ideal for me to carry out my project throughout the course of my undergraduate education. In addition, Dr. Gallagher, a well-known expert in animal memory system and drug development, would be invaluable to help shepherd me through this work. A Woodrow Wilson Research Fellowship would provide me with the necessary resources to begin this work to develop effective therapeutics for cognition to help individuals with schizophrenia, and I anticipate a valuable experience.

### References

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