

**Pharmacologic Modulation of Hippocampal Activity in Psychosis**

**Stephan Heckers, MD MSc  
Professor and Chair  
Department of Psychiatry and Behavioral Sciences  
Vanderbilt University Medical Center  
1601 23<sup>rd</sup> Ave. S Suite 3060  
Nashville, TN 37212**

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## 1.0 BACKGROUND

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The purpose of this study is to test whether administration of levetiracetam (LEV), a commonly used anti-epileptic that alters neurotransmitter release, can reduce hippocampal hyperactivity. Specifically, we will utilize two functional magnetic resonance imaging (MRI) techniques: 1) blood oxygen level dependence (BOLD) contrast will assess activity with a visual scene processing task that engages the anterior hippocampus and 2) arterial spin labeling (ASL) will assess baseline activity. This study will also assess whether patients have improvement in their symptoms after receiving LEV. Previous studies in people with psychotic disorders have shown that the hippocampus is hyperactive and more activity correlates with worsening of clinical symptoms. Therefore, the aim of this study is to use an intervention to further understand the underlying mechanisms of the hippocampus in psychosis.

### Background and Significance

The lifetime prevalence of schizophrenia is about 0.7% (Saha et al., 2005), and the burden of illness is significant not only for patients but also society at large (Lehman et al., 2004). One contribution to this massive disease burden is the lack of optimal treatments, as only 20% of diagnosed individuals reach favorable treatment outcomes (Association, 2016). An important factor in the lack of treatment development for psychotic disorders is the unavailability of predictors that can be used to determine if therapeutic candidates elicit their targeted biological effects (Tregellas, 2014).

A growing body of literature demonstrates that the anterior hippocampus is hyperactive in patients with schizophrenia (Schobel et al., 2009; Talati et al., 2014) and clinical high risk patients that progress to developing schizophrenia (Modinos et al., 2018; Schobel et al., 2013). This hyperactivity is the result of an excitation-inhibition imbalance in the hippocampus (Heckers and Konradi, 2015; Uhlhaas, 2013). Excitatory, glutamatergic pyramidal cells comprise 90% of hippocampus neurons (Olbrich and Braak, 1985). The remaining neurons are inhibitory, GABAergic interneurons that modulate and synchronize overall activity to exert ultimate hippocampus activity (Freund, 2003; Klausberger and Somogyi, 2008). Different models have attributed the hippocampal excitation-inhibition imbalance to alterations in neurotransmitters glutamate or GABA (Benes, 1999; Stan et al., 2015) or interneuron abnormalities (Heckers and Konradi, 2015; Lodge et al., 2009).

**This human laboratory study seeks to use an intervention to further understand the underlying mechanisms of the hippocampus in psychosis.** This will be accomplished by using LEV. While the exact mechanism of action of LEV continues to be evaluated, evidence shows that it regulates neuronal synaptic exocytosis and calcium-induced neurotransmitter release (Lynch et al., 2004). Therefore, LEV may have a therapeutic effect on excitation-inhibition imbalance of the hippocampus. LEV has an overwhelming amount of evidence for modulating neuronal activity and has been established as a FDA-approved anti-epileptic drug for almost two decades (Lyseng-Williamson, 2011). Most other anti-epileptic medications affect ion channels, which are functionally "upstream" from synaptic exocytosis. Because of this, LEV has a more favorable side-effect profile when compared to other FDA-approved anti-epileptic drugs. Additionally, LEV has a lower risk of pharmacokinetic interactions with antipsychotics, and a lower risk of cognitive side effects when compared to other anti-epileptic drugs (Patsalos, 2000).

Neuroimaging studies provide the best opportunity to test the hypothesis of an excitation-inhibition imbalance in the hippocampus (Logothetis, 2008). Our lab has recently developed a functional MRI task that allows for robust, individual-subject level analysis of the hippocampus (McHugo et al., 2019). Based on the evidence provided above, LEV is an ideal intervention to assess hippocampal activity. Because hippocampal activity correlates to clinical symptoms (Friston et al., 1992; Gur et al., 1995; Liddle et al., 1992), can predict clinical progression, has translational capabilities (Gozzi et al., 2010, 2008; Stevens and Wear, 1997), and has recently been shown to function as a therapeutic target for schizophrenia (Bakker et al., 2012; Gill and Grace,

2014; Gomes et al., 2016; Koh et al., 2018; Perez and Lodge, 2014; Smucny and Tregellas, 2017), it is an ideal neural mechanism to study.

## 2.0 RATIONALE AND SPECIFIC AIMS

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**Our central hypothesis is that in psychotic disorders, LEV will safely normalize hippocampal hyperactivity.** This will result in an increase in recruitment and activity of the hippocampus during tasks that specifically engage the hippocampus. Secondly, we hypothesize that LEV will improve the symptomatology of psychotic disorders. In this project, we will test our hypothesis in 30 psychotic patients and 30 healthy control subjects. Following baseline clinical assessments, neuropsychological testing, and neuroimaging, participants will receive an initial dose of LEV. At this time they will undergo a second neuroimaging procedure. After the second brain imaging study, they will begin two weeks of oral LEV. Finally, participants will repeat all testing at the end of the 2-week study period, to allow us to assess the effects of a LEV intervention.

**Primary Aim: To determine whether administration of oral LEV over two weeks modulates hippocampal hyperactivity**

Hypothesis 1: Oral LEV will decrease, in a dose-response relationship, hippocampal activity in healthy control subjects and psychotic patients (ASL study).

Hypothesis 2: Oral LEV will normalize hippocampal recruitment in patients (Scene-processing fMRI study).

Hypothesis 3: Compared with healthy control subjects, psychotic patients will show higher hippocampal activity (ASL study) and reduced hippocampal recruitment (Scene-processing fMRI study).

**Secondary Aim: To determine whether administration of oral LEV over two weeks improves clinical symptoms in patients with psychotic disorders**

Hypothesis 1: Oral LEV will improve cognitive symptoms in psychotic patients (eye-tracking relational memory task).

Hypothesis 2: Oral LEV will reduce positive and negative psychotic symptom severity (Positive and Negative Syndrome Scale, PANSS).

## 3.0 ANIMAL STUDIES AND PREVIOUS HUMAN STUDIES

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### 3.1 Animal Studies:

Animal models have been used to study the relationship between hippocampal activity and variety of different diseases and conditions. Treatment with LEV has been found to improve memory in both aging (Devi and Ohno, 2013; Koh et al., 2010; Suberbielle et al., 2013) and Alzheimer's disease (Devi and Ohno, 2013; Hall et al., 2015; Sanchez et al., 2012; Suberbielle et al., 2013) animal models that are associated with increased neural activity in the hippocampus.

Importantly, all of these studies used doses substantially lower than those used in seizure models. Koh et al. (2010) demonstrated improvements in spatial memory task performance at both 5 and 10 mg/kg. Typical antiepileptic doses of LEV in rodent seizure models are in a range of 50-150 mg/kg. Devi and Ohno (2013) used 10-20 mg/kg to improve memory in a contextual fear conditioning paradigm. Hall et al. (2015) used a dose of 75 mg/kg/day to reverse ion channel depletion associated with hippocampal dendritic hyperexcitability and to reverse abnormalities in a spatial memory behavioral task. Suberbielle et al. (2013) also used 75 mg/kg/day to demonstrate improvements in learning and memory. Sanchez et al. (2012) reported that LEV loses both its antiepileptic effect and its beneficial effect on behavioral and molecular abnormalities in mice when given at high doses. Only low doses of LEV reversed learning and memory abnormalities and abnormal

alterations in the expression of synaptic activity. Importantly, of seven FDA-approved anti-epileptics tested with differing methods of action, only LEV had this effect (Sanchez et al., 2012).

Treatment with LEV in animal models of schizophrenia has also demonstrated improvements in cognitive symptoms. The inability to filter brain responses to repetitive stimuli, as evidenced by poor inhibition of early (50 ms post-stimulus) evoked brain response to the second of two closely paired, identical auditory click stimuli is a feature of schizophrenia (Potter et al., 2006). This is measured in preclinical models using in vivo recordings of auditory-evoked potentials from the mouse hippocampus. Drugs that improve gating in rodents have demonstrated similar effects in human patients, supporting the utility of this gating model as a translational tool (Olincy and Stevens, 2007). A 10 mg/kg dose of LEV was found to improve auditory gating in a mouse model of schizophrenia (Smucny et al., 2015).

A more recent study tested LEV's ability, alongside and in combination with the antipsychotic risperidone, to alleviate memory impairment in an animal model of schizophrenia that recapitulates neural hyperactivity and memory problems similar to those seen in schizophrenia patients (Koh et al., 2018). LEV, but not risperidone, improved memory performance dose-dependently in a hippocampal-dependent memory task. Furthermore, LEV remained effective when administered concurrently with risperidone, providing evidence that LEV could be used as adjunctive therapy to treat the cognitive deficits in schizophrenia patients with antipsychotic therapy.

### **3.2. Human Studies:**

An extensive amount of research has been done in humans for LEV to obtain FDA-approval as an anti-epileptic drug. There are currently no studies that have published results investigating the effect of LEV in schizophrenia patients. However, two NIMH-supported studies using LEV in schizophrenia patients are currently under way [PI: Goff, D., NCT03129360; PI: Tregellas, J., NCT NCT02647437]. In addition, there are, to the best of our knowledge, five studies using human imaging techniques that have investigated the effects of LEV on brain activity (Bakker et al., 2015, 2012; Wandschneider et al., 2014; Zhang et al., 2018, 2017).

Bakker et al. (2012) studied a population of amnesic mild cognitive impairment (aMCI) patients with hippocampal hyperactivity. This study employed a longitudinal, randomized, placebo-controlled crossover design that required aMCI patients to take 2 weeks of LEV. By using a low dose of LEV (125 mg BID), hippocampal activation in the aMCI group was reduced to a level that did not differ from healthy controls using fMRI. Additionally, aMCI patients taking LEV significantly improved their performance in a hippocampal-dependent memory MRI task when compared to aMCI patients taking a placebo. A follow-up study (Bakker et al., 2015) using the same study design, including utilizing fMRI to investigate hippocampal activation and a hippocampal-dependent memory task replicated this finding. Altogether, these results suggest that LEV may have clinical benefit in disease populations other than epilepsy at doses much lower than typically given (Smucny et al., 2015).

Wandschneider et al. (2014) studied a population of patients with temporal lobe epilepsy (TLE). This population has previously been shown to be unable to deactivate their diseased hippocampi with increasing cognitive demands (Stretton et al., 2012). In a retrospective study design, about 55% of TLE patients received varying doses of LEV (median (interquartile range) = 2,500 mg/day (1,000)) in addition to other anti-epileptic drugs. Patients on LEV showed normalization of functional network deactivations in the right temporal lobe in right TLE during a right-lateralizing visual-spatial task, and in the left temporal lobe during a verbal task. Post-hoc analysis showed that both hippocampi were more abnormally activated in patients with lower doses. These findings suggest that LEV is associated with restoration of normal activation patterns in the hippocampus.

Two additional studies have used LEV as an intervention in a fMRI study in epilepsy patients (Zhang et al., 2018, 2017). Although they did not employ cognitive tasks in the fMRI study, we highlight them here to demonstrate that fMRI is sufficient tool to detect group level changes with an intervention of LEV.

## **4.0 INCLUSION/EXCLUSION CRITERIA**

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### **Inclusion criteria for psychosis subjects**

1. Men and women age 18 - 65.
2. Communicative in English.
3. Provide voluntary, written informed consent.
4. Physically healthy by medical history.
5. BMI > 17.5 and < 45.
6. Diagnosis of a psychotic disorder confirmed by Structured Clinical Interview for DSM-V (SCID) or diagnostic interview with a trained clinician.
7. Stable medication regimen over at least the past two weeks, including the use of either an oral or intramuscular administration of an antipsychotic medication.
8. For females, no longer of child-bearing potential, or agreeing to practice effective contraception during the study (e.g., established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device [IUD] or intrauterine system [IUS]; barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository; male partner sterilization; or true abstinence when this is in line with the preferred and usual lifestyle of the subject); and,
9. For females of child-bearing potential, must have negative urine pregnancy test at time of screening visit and before each testing day.
10. Not breastfeeding/nursing at time of screening or at any time during the study.

### **Exclusion criteria for psychosis subjects**

1. Age less than 18 or greater than 65.
2. Not communicative in English.
3. Unable to provide written informed consent.
4. Current medical or neurological illness.
5. History of severe head trauma.
6. BMI < 17.5 or > 45.
7. Meets criteria for diagnosis of substance or alcohol use disorder within the past month.
8. Positive urine pregnancy test at time of screening, before each testing day, or any potential concern for pregnancy at any time during the study.
9. Breastfeeding/nursing at time of screening or at any time during the study.
10. Conditions that preclude MR scanning (as defined in the Screening Form)
11. Conditions that preclude study drug administration (as defined in the Screening Form)

### **Inclusion criteria for healthy controls**

All of the above except for subjects will be psychiatrically healthy and not taking psychotropic or potentially psychoactive prescription medication.

### **Exclusion criteria for healthy controls**

All of the above and in addition:

1. Current use of psychotropic or potentially psychoactive prescription medication.
2. Major psychiatric disorder as determined by DSM-V (major depression, bipolar disorder, obsessive compulsive disorder, post-traumatic stress disorder, etc)

## **5.0 ENROLLMENT**

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**5.1. Recruitment:** Study participants will be recruited from the following sources:

**5.1.a Psychiatric Genotype/Phenotype Repository (PGPR, IRB #080606):** The PGPR study includes a clinical interview during which diagnostic and clinical history data is collected. At the end of this interview, individuals will be asked by one of the key research personnel listed on this application if they are interested in participating in the study. The PI of this study is the same PI for the PGPR study. Subjects will be read a script describing the study. Subjects will be told that the study is separate from their participation in the PGPR study and choosing not to participate in the study will not affect their participation in the PGPR study. In addition, individuals that have previously completed the PGPR study may be contacted and asked if they would like to participate in the study. The consent form for the PGPR study states that subjects may be contacted and asked if they would like to take part in future studies, if they agree. Subjects will be read a script telling them about the study. The telephone screening form used for the Psychiatric Genotype/Phenotype study will be re-administered to make sure that they still meet the original criteria for participating in the Psychiatric Genotype/Phenotype Study (i.e. age, physical health, and MRI requirements).

**5.1.b Vanderbilt Psychiatric Hospital and Adult Outpatient Clinic:** Adult individuals who will likely meet criteria for one of the proposed study diagnoses (as determined by chart review, participation in another clinic study, etc.) will be approached by their treatment provider (or Research Assistant if they are participating in another study) to see if they are willing to discuss participation in this study. If the patient assents, their name will be given to a research staff member who will make contact with them to schedule a meeting. At the meeting, the purpose of the study, specific procedures, risks, and inclusion and exclusion criteria will be discussed with the subject. The informed consent form will be reviewed with the subject. The subject will be encouraged to carefully read the consent form and ask questions. The subject will then undergo an informed consent survey to ensure that he or she understands the consent form. After written informed consent is obtained, Study Procedures will be performed.

**5.1.c Greater Nashville Area:** Individuals who may meet criteria for one of the proposed study diagnoses (as determined by self-identification) and healthy non-psychiatric control subjects will be recruited through mass email ads through the Vanderbilt University Medical Center email system, study advertisements distributed/posted in the community, Vanderbilt General Clinical Research normal volunteer program, the Vanderbilt Kennedy Center, and mass email ads through the Vanderbilt University Medical Center email system. If potential subjects are interested in participating in this study and appear to meet inclusion and exclusion criteria (based on initial screening), a meeting with the RA will be scheduled. At this meeting, the informed consent form will be reviewed with the subject. The subject will be encouraged to carefully read the consent form and ask questions. If the subject appears to meet inclusion and exclusion criteria and wishes to participate in this study, informed consent will be obtained, and Study Procedures will be performed.

**5.2 Monetary Compensation:** All study subjects will be remunerated \$25 for completion of the screening and consent visit, regardless of their decision to enroll in the study or their eligibility to enroll. Because of the study design, subjects only yield meaningful primary outcome data if they complete the long-term intervention phase session. They will therefore be compensated an additional \$475 at the completion of the remaining study visits. This incentivization is designed to yield greater benefit from the research, thereby improving the risk/benefit ratio of the study.

**5.3 Recruitment:** We will make every effort to recruit equal numbers of men and women. We will not exclude subjects based on gender or minority status. We minimize coercion throughout the study by repeatedly informing subjects that they may discontinue study procedures at any point, or opt-out of any specific part of the study they become uncomfortable with completing.

We plan to recruit up to 60 subjects (up to 30 healthy control subjects and up to 30 patients with psychotic disorders) for the study. We hope to acquire analyzable data from at least 20 control subjects and 20 patients.

Subjects who were recently recruited in other psychiatry studies also conducted by this PI (e.g. genotype/phenotype studies) may not be required to participate in components of this study that would duplicate efforts (e.g. SCID interview). We plan to include data from those studies in the analyses of data from this study. Participants will be compensated for all activities they complete.

## 6.0 STUDY PROCEDURES

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**Overview:** There are nine components of the study:

1. Screening and Consent
2. Diagnostic Interview
3. Clinical Assessment (psychosis patients only)
4. Neurocognitive Assessment
5. MRI Scanning
6. Drug Administration
7. Blood draws
8. Urine pregnancy test
9. Mid-intervention phone call

Each component will be described in detail below. The entire study will be completed in about two weeks. The number of study visits depends on whether the planned study procedures can be completed in the specified time period and the availability of both the participant and necessary resources (i.e. availability of the MRI scanner). The specific rating scales completed will be dependent upon diagnosis and the time since an individual participated in the PGPR study, as many of the measures overlap and assess symptomatology based on specific time-intervals (i.e., the last 2 weeks).

**6.1 Screening and Consent:** Subjects will be asked if they would like to participate in the current study. This screening will occur over the phone or in person using the Screening Form. Informed consent will be obtained by study personnel directly involved in the research (i.e. research staff or graduate student). Personnel have completed IRB training and have considerable experience running studies on psychiatric populations. Informed consent will be obtained in the research offices at the Psychiatric Neuroimaging Program. A research staff member will explain the applicable procedures and the possible risks and benefits to the subjects. The details of the informed consent procedure are as follows:

1. The investigator or research staff and the subject will read together the entire consent form
2. The subject will be asked details about the study. To document that the subject has read the consent form and has the capacity to understand the most important details, the investigator will use the appropriate Informed Consent Survey. The questions will be read by the investigator or research staff and the answers will be recorded (appropriate response listed in *Italics* in the Informed Consent Survey). If the subject is unable to answer any of the questions, or if the subject demonstrates a lack of understanding, the investigator or research staff member will then review the details of the study again. Subjects who are unable to answer the questions, even after additional information is provided, will be excluded from the study.
3. The subject will be informed that regardless of whether or not they take part in this research study, it will not affect their treatment, payment or enrollment in any health plans or affect their ability to get benefits or care in any way.
4. The subject will be provided with copies of the signed consent form and the Informed Consent Survey (including the answers given) at the time of the initial visit.

It will be emphasized to all subjects that their participation is completely voluntary, and that even after signing the consent document they are still free to withdraw from the study at any time; in which case they will be compensated for the portion(s) of the protocol they did complete.



**6.2 Diagnostic Assessment:** Under the supervision of the PI, a trained research assistant will administer the Structured Clinical Interview for DSM-V (SCID), a clinician-rated assessment of psychiatric disorder. Diagnoses are made both for current and lifetime periods. The SCID is reliable and valid in psychiatric populations (significantly superior to standard clinical interview). We will supplement the SCID with the psychotic disorders module from the Diagnostic Interview for Genetics Studies (DIGS), which provides more information for the accurate differential diagnosis of psychotic disorders. The Informed Consent Form will include check box indicating if the study participant is being asked to complete the Diagnostic Interview.

As stated previously, subjects who were recently recruited in other psychiatry studies also conducted by this PI (PGPR) may not be required to participate in components of this study that would duplicate efforts (e.g. SCID interview). We plan to include data from those studies in the analyses of data from this study. If an excessive time has passed since an individual participated in a PGPR study, portions of the diagnostic interview may be re-administered to determine if there have been any interval changes in a patient's diagnostic status.

**6.3 Clinical Assessment (individuals with psychosis only):** Almost all of the clinical and cognitive tests have been used in our past studies. They are not burdensome and we allow breaks. All scales will be completed before or on the day of the neuroimaging procedures. All patients are asked to review their substance abuse and current medications at every visit. The clinical assessments will be completed twice in this study (baseline assessment and after two week intervention).

**6.3.a Structured Clinical Interview for DSM-5 (SCID):** A research staff member is trained to administer the Structured Clinical Interview for DSM-V (SCID) (First, 2015), a clinician-rated assessment of psychiatric disorder. Diagnoses are made both for current and lifetime periods. The SCID is reliable and valid in psychiatric populations, with coefficients of agreement between .70 and 1.0 for depressive, anxiety, and substance use disorders (significantly superior to standard clinical interview). If significant suicidal thought is noted during the evaluation, the patients will be encouraged to talk to their treatment providers. If the patient is judged to be at imminent risk of self- or other-harm, standard procedures in the clinics will be followed. The SCID can take from 30 minutes to several hours to complete.

**6.3.b Hamilton Depression Rating Scale (HAM-D):** Administered by a clinician or rater in order to gather data about symptoms independent of the biases inherent in self-report. The version of the HAM-D (Hamilton, 1960) used here incorporates atypical symptoms. It has been used by our group in previous studies, and has been associated with excellent reliability. We will also be using a measure to assess suicidal history and behavior which was developed internally and is composed of questions which would be assessed in any clinical interview. This assessment takes about 15-20 minutes to complete.

**6.3.c Positive and Negative Syndrome Scale (PANSS):** a 30-item clinician-rated scale designed to rate both presence of active psychotic symptoms and of cognitive symptoms, like alogia, anhedonia, and flattened affect (Kay et al., 1987). This measure has fair to good psychometrics (Peralta and Cuesta, 1994) and takes about one hour to complete.

**6.3.d Personal and Social Performance Scale (PSP):** Administered to assess patient's functioning in four main areas: 1) socially useful activities; 2) personal and social relationships; 3) self-care; and 4) disturbing and aggressive behaviors. This measure has high reliability and takes about 5 minutes to complete (Morosini et al., 2000).

**6.3.e Young Mania Rating Scale (YMRS):** an 11-item clinician-rated measure of manic symptoms. Items are rated on various scales using pre-defined anchors ranging from absent to severe. The measure has adequate psychometrics and takes about 20 minutes to complete (Young et al., 1978).

**6.3.f Side Effects and Treatment Compliance:** Side effects are assessed using the Veterans Administration neurotoxicity rating scale (VANRS) (Cramer et al., 1983). This scale is used to quantify impairment of change in neurological status and systemic toxicities in patients starting an antiepileptic drug in the setting of a clinical trial (Perucca and Gilliam, 2012). Compliance is assessed with a medication count and the Medication Adherence Questionnaire (MAQ) (Morisky et al., 1986). Altogether, these assessments should take less than 20 minutes to complete.

**6.4 Cognitive Assessment:** Subjects will be asked to complete a relational memory experimental study. Subjects will be taken to a private interview room in the offices of the Psychiatric Neuroimaging Program. Eye tracking equipment will be used during the study to record eye movement behavior (ISCAN, Inc.). The eye tracking system uses a headmounted camera to track the subject's pupils in relation to a computer screen placed in front of the subject. Subjects will be shown the eye tracking system and given a brief explanation of the headmounted camera. The camera will be placed on the subject's head and the system software will be calibrated to the individual's pupil according to software specifications. Software may be recalibrated between each block of images to ensure accurate eye tracking. Subjects will view face and scene image pairs on a computer screen while eye movements are tracked. Faces and scenes will be drawn from a standard set of images which have been used in similar research studies (Hannula et al., 2010). Faces and scenes will be shown in color. Faces and scenes used are considered neutral, in that they should not elicit strong emotions (i.e., fear, anxiety, happiness). Subjects will be told to study each face/scene pair so that they can later identify a match between a particular face and scene. Subjects will view multiple blocks of face/scene pairs during the familiarization phase. During the testing phase, subjects will be shown blocks of previously seen scene images with multiple faces overlaid on the image. Subjects will be asked to choose the face previously related to the scene by button press while eye movements are tracked. Subjects will be fully debriefed following completion of all test phase blocks. Faces and scenes will be randomized to lists, and lists will be rotated and counterbalanced across subjects to ensure that each scene is paired equally with each face across the study. The relational memory experimental paradigm will require up to 1 hour, including calibration of the eye tracking software. There will be a total of two cognitive assessments in this study (baseline assessment and after two-week intervention).

**6.5 MRI Procedures:** MRI scans of the brain will be obtained using the MRI scanners in the Center for Human Studies in the Vanderbilt University Institute for Imaging Science (VUIIS), located in the Vanderbilt Hospital and Medical Center North. This will require approximately 60-90 minutes. There will be a total of three MRI scans in this study (baseline assessment, two hours after the initial LEV dose, and after two-week intervention of LEV).

**6.5.a MRI Screening:** The participant will fill out the MRI Procedure Screening Form. The purpose of this form is to ensure that there are no implanted medical devices or metals that could injure the subject if exposed to a high magnetic field. This form will be filled out in a private room adjacent to the MRI scanner and reviewed by the MR Technologist and the research assistant.

**6.5.b Scanning Procedures:** Imaging studies will take place on a Phillips 3.0 T MRI scanner. The magnet and the magnet's control console are in separate rooms, but the investigator and the subject will be in voice communication at all times, and the investigator will be able to see the subject through a window. All data acquired on the scanner will be securely transferred over the Vanderbilt network to the Institute of Imaging Science's server. Imaging data will be de-identified and only be accessible to the PI, co-investigators, and VUIIS personnel. Scanning procedures may include: 1) Structural imaging, 2) Resting state functional imaging, 3) ASL imaging to non-invasively measure cerebral blood flow, and 4) Functional imaging with task – while in the scanner, participants will view images that include faces,

objects and scenes. Images are projected to a mirror above the participants head from a projector located outside the scanner room. Some runs will repeat the same face or object, some runs will present different images. Participants will complete between 1-8 runs of this task. To maximize participant's attention to the images, participants will be instructed to push a button to detect targets. Targets may include image repeats or changes in the image (e.g., image size). This task is similar to the reported in McHugo et al., 2019.

**6.6 Study Drug Administration:** After completing the baseline clinical assessment, cognitive assessment, and MRI, eligible participants will be instructed to take their first dose of 500 mg LEV. After a two hour time window, the participants will complete the same MRI battery. After the second MRI, patients will begin a 2-week intervention with 250 mg BID oral LEV. Clinical assessment, cognitive assessment, and MRI will be repeated after this 2-week intervention phase.

**6.6.a Dosage Rationale:** We selected 250 mg BID dosage because of other studies that have been able to safely demonstrate changes in cognitive performance and changes in hippocampal activation (Bakker et al., 2015, 2012) using dosages of LEV intervention in patient cohorts outside the FDA-approved indications for LEV. This dosage is well below the typical ranges for efficacy as an antiepileptic with doses of 1,000-3,000 mg/day. Studies using a dosage of 125 mg BID have reported drug levels to be 4.4 mcg/ml +/- 0.53 (mean and SEM), while dosages of 1,000-3,000 mg/day achieve levels of 10-40 mcg/ml (Bakker et al., 2015, 2012; Lyseng-Williamson, 2011). Human results indicating effects with lower dosages are consistent with the animal literature. Studies that have targeted rats with cognitive impairment and excess hippocampal activity have demonstrated improvements in memory performance using a dosage of 10 mg/kg (Koh et al., 2018, 2010). In another animal model of schizophrenia, dosages of 10 mg/kg improved a sensory gating task performance (Smucny et al., 2015). Typical antiepileptic doses of LEV in rodent seizure models are in a range of 50-150 mg/kg (Ji-Qun et al., 2005; Stratton et al., 2003).

**6.6.b. Timing Rationale:** We selected a two-hour duration for the first imaging assessment based on LEV's absorption and clearance data. The pharmacokinetics will be reviewed in more detail in sections 7.2 and 7.3. Briefly, LEV is rapidly and almost completely absorbed after oral administration, with peak serum concentrations occurring approximately one hour after dose (Gambardella et al., 2008). Based on a study that measured LEV plasma concentrations ( $\mu\text{mol/L}$ ) over time after oral ingestion of varying doses of LEV (500-5000mg) in healthy volunteers, LEV levels will be approximately 9.75 mcg/mL (57.3  $\mu\text{mol/L}$ ) at two hours (Patsalos, 2004). Therefore, two hours after LEV administration is the earliest time-point where we can assess study participants at a sub-therapeutic epilepsy dose (10-40 mcg/mL) of LEV (Bakker et al., 2015, 2012; Lyseng-Williamson, 2011).

**6.6.c Duration Rationale:** We selected a 2-week duration because of other studies that have been able to safely demonstrate changes in cognitive performance and changes in hippocampal activation (Bakker et al., 2015, 2012) after 2 weeks of LEV intervention in patient cohorts outside the FDA-approved indications for LEV.

**6.6.d Compliance:** We will assess compliance using the Medication Adherence Questionnaire, a medication count after two weeks, and a test for LEV blood levels.

**6.6.e Concomitant medications:** We will allow concomitant use of any medication approved by the US FDA unless specified in our inclusion/exclusion criteria (e.g. normal controls using psychotropic medications). Reviews have indicated that LEV does not affect the metabolism of other drugs, including antipsychotics (Besang and Berry, 2006).

**6.7 Blood Draw:** Subjects will undergo three separate blood draws. The first blood draw will occur during the

Screening and Enrollment visit. The second blood draw will occur during the short-term intervention assessment. The third blood draw will occur during the long-term intervention assessment. Both visits will use blood draws to assess GFR and CBC, as addressed in the study drug risks below. During the short-term intervention visit, we will check LEV levels for the study of a dose-response relationship with blood flow. During the long-term intervention visit, participants will undergo a blood draw to check LEV levels to ensure compliance with taking the study medication.

**6.8 Urine pregnancy test:** All females will be required to take a urine pregnancy test during the screening and enrollment visit, baseline visit, and two-week follow-up visit, as addressed in the study drug risks below.

**6.9 Mid-Intervention Phone Call:** After the visit where LEV is administered and before the two week follow-up visit, we will call the participant. This will be to **1)** ensure that they are taking the study medication as prescribed and remind them to continue to do so. **2)** Ask about any issues or side effects they may be experiencing because of the study. We believe this phone call will increase the likelihood that participants complete the study and will help us identify any side effect complications earlier.

## **7.0 RISKS - STUDY DRUG**

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**7.1 Risks:** Side effects of LEV exposure have been well characterized in clinical trials using LEV dose ranges of 1000-3000 mg/day. The most common symptoms are neurological, including somnolence (15% of patients), asthenia (15%), headache (14%), dizziness (13%), and ataxia (3%) (Ben-Menachem and Falter, 2000; Cereghino et al., 2000; Shorvon et al., 2000). Patients also reported a slightly higher incidence of infection (13% of patients). Up to 13% of patients also experienced adverse neuropsychiatric symptoms. In most of these patients, the symptoms have been mild, including agitation, hostility, apathy, anxiety, emotional lability, and depression (Gambardella et al., 2008). About 1% of patients have experienced serious neuropsychiatric symptoms including hallucinations, suicidal ideations, or psychosis (Kossoff et al., 2001; Mula et al., 2003). In these reports, symptoms occurred mostly within the first month of therapy. Dose reduction or discontinuation has led to resolution of symptoms in cases reported. Conversely, LEV has no major adverse effects on cognitive function (Neyens et al., 1995), which is an improvement over more traditional anti-epileptic agents (Dooley and Plosker, 2000). Presently, there are no sufficient data to recommend treatment with LEV during pregnancy. Case reports have indicated Stevens-Johnson Syndrome (SJS) is an exceedingly rare side effect of LEV administration (Zou et al., 2012). In a meta-analysis of 26 double-blind, randomized, placebo-controlled trials (2832 patients), no dose-response relationship was found for any side effects (Verrotti et al., 2015).

**7.2 Absorption and Distribution:** LEV is rapidly and almost completely (>95%) absorbed (Rossetti and Bromfield, 2005) after oral administration of doses ranging from 250 to 5000 mg, with peak serum concentrations occurring approximately 1 hour after dose and steady state concentrations are reached within 48 hours (Gambardella et al., 2008). The oral bioavailability of LEV tablets is 100%. Food does not affect the absorption of LEV. The volume of distribution is 0.5-0.7 L/kg (Patsalos, 2004). LEV does not bind to plasma proteins and has linear pharmacokinetics that are time-invariant with low intra- and inter-subject variability (Patsalos, 2004, 2000).

**7.3 Metabolism and Elimination:** LEV is not extensively metabolized in humans. The major metabolic pathway is the enzymatic hydrolysis of the acetamide group by a plasma hydroxylase. This produces the inactive compound carboxylic acid metabolite ucb L057 (24% of dose). LEV does not undergo hepatic metabolism (Nicolas et al., 1999). The serum half-life is 6 to 8 hours (Krasowski, 2010). LEV is eliminated from systemic circulation by renal excretion as unchanged drug (66% of the dose). Total body clearance is 0.96 mL/min/kg and renal clearance is 0.6 mL/min/kg. The metabolite ucb L057 is renally excreted with a renal clearance of 4 mL/min/kg. Clearance is rapid, so that within 48 hours approximately 93% of an oral dose is eliminated. In patients with renal impairment, doses should be reduced in accordance with creatinine clearance (Patsalos, 2004).

**7.4 Interactions with other Drugs:** Reviews have indicated that LEV does not affect the metabolism of other drugs, including antipsychotics (Besag and Berry, 2006).

#### **7.5 Minimizing Risk for Study Drug:**

**7.5.a Dosage:** As mentioned above, clinical indications for LEV use in epilepsy range from 1000-3000 mg/day. Our study will be using 250 mg BID. As reviewed in both section **3.0** and **6.6.b**, human functional MRI studies have demonstrated that low doses decrease hippocampal activity and improve memory task performance in patient cohorts outside the FDA-approved indications for LEV.

**7.5.b Screening Process:** The screening visit will include a Screening Form that has a LEV Screening section. It will assess neuropsychological history to address the neuropsychological side effects and assess history of rashes in response to medications to address the possibility of a SJS reaction. Additionally, a blood draw to obtain a CBC and BMP will assess creatinine levels, to address renal function, and white blood count, to address possibility of infection, in each patient at each visit. Blood draws for a CBC and BMP will not occur if there is a record of recent CBC or BMP values (within past 45 days). Lastly, females will perform a pregnancy test at each visit to ensure no teratogenic effects.

**7.5.c Usage as add-on therapy for psychosis cohort:** LEV has no known major drug interactions. Therefore, the psychosis cohort will use LEV as an add-on therapy with the antipsychotic medications.

**7.5.d Driving after drug administration:** Because somnolence is a major side effect of LEV, we require that participants who drive themselves to Vanderbilt Psychiatric Hospital on Day 1 (first day of drug administration) will take a Standardized Field Sobriety Test to ensure they are safe to drive themselves home. This test is based on available data provided by the National Highway Traffic Safety Administration. It will be administered before initial drug administration and as the final assessment on Day 1 immediately before the participant leaves. It takes about 5 minutes to complete. If the participant scores above an impairment threshold on any portion of the test, we will purchase a car service (Uber/Lyft) to drive the participant home and back to Vanderbilt Psychiatric Hospital on another day to obtain their vehicle.

**7.6 Risk/Benefit Ratio:** When the safety record outlined above is considered, the risks of participation in this study are low. Long-term safety of LEV appears to be very favorable. Subjects participating in these studies will receive MRI assessment and basic drug and pregnancy screening (when applicable) at no cost to them. Otherwise, there are no direct benefits to the subjects participating in this research. The long-term potential benefit of this study is a mechanistically directed approach toward identifying a reliable biomarker for psychotic disorders. Every research study requires the potential benefits to outweigh the potential risks of the study. The potential benefit of establishing a biomarker is significant for public health, including for patients, their families, communities, and healthcare systems. While the study procedure confers greater than minimal risk, the low likelihood of serious adverse effects is outweighed by the potential public health benefits stemming from the potential results of this study and subsequent studies based on these results.

With respect to MRI scanning, the MR system requires the use of rapidly varying magnetic gradient fields and strong radio frequency fields. These switched gradient and radio frequency fields conform to the guidelines established by the US FDA for time varying magnetic fields in MR devices. No serious or lasting incidents or side effects associated with the use of high field magnets have been reported. Based on this experience, and valid scientific evidence, the FDA has found that this does not pose a significant risk to human subjects.

#### **8.0 RISKS – OTHER THAN THE STUDY DRUG**

**8.1 Psychological and Behavioral Assessment Risks:** At screening, subjects will undergo non-invasive

psychological assessment of a structured nature that has been consistently used without adverse effects in previous studies with a similar subject population. There is the potential risk that subjects may become fatigued during the performance of screening assessments or behavioral tasks, and that discussion of personal issues with study personnel in the context of screening issues may be stressful or uncomfortable. Because subjects participating in this study will be stable outpatients, it is unlikely that the stress posed by such measures will exacerbate baseline psychiatric symptoms.

**Minimizing the Risk of Psychological and Behavioral Assessment:** The risk of the diagnostic evaluation involves the possibility that participants may be asked questions which cause them distress. These would be questions consistent with any clinical evaluation. In order to address this risk, participants will be told they can decline to answer any questions and can stop the evaluation at any time.

## **8.2 MRI Scan Risk:**

1. Ferromagnetic objects brought into the room will be pulled toward the magnet.
2. Due to the magnetic properties of the scanner, if a subject has implanted metal or medical devices they may experience abnormal torques or failure to function properly. This may cause injury to the body areas where the device is located.
3. There is a risk of tissue heating if there is excessive power deposition of radiofrequency (RF) magnetic waves. Excessive RF waves emitted could cause the atoms to transmit high-frequency RF wave at such a rate as to cause the neighboring tissue to heat.
4. There is a risk of peripheral nerve stimulation if gradients are switched too rapidly. Switching a gradient will increase the magnetic field strength in specific area. This in turn, increases the current in that area. If the field strength is switched too rapidly, the amount of current will increase to the point of tissue excitation.
5. The subjects may experience a claustrophobic reaction in the magnet.
6. There are loud banging noises with MR imaging that may be uncomfortable.

## **Regarding the MRI procedures we will employ the following protections:**

1. The subject will be instructed not to bring metal objects into the magnet room and will be provided with lockable facilities for personal belongings.
2. The use of the MRI screening form will exclude from the study potential subjects with implanted metal or medical devices.
3. The FDA has strict limits regarding power deposition. Safeguards built into the operating system prevent exceeding those limits.
4. The FDA has strict limits regarding gradients strengths and rise times. Safeguards built into the operating system prevent exceeding those limits.
5. Subjects will be warned of the potential for claustrophobic reactions and those with a prior history of such reactions will be excluded from the study. If a subject experiences an unexpected and severe claustrophobic reaction, the study will be terminated.
6. Subjects will be provided with hearing protection.

**Potential Risks to Subjects (Rare/Unforeseen):** There have been no appropriate studies that either rule out or demonstrate negative health effects of MRI on fetuses. We will inform women with child-bearing potential of this information and pregnant women will not be allowed to participate. If new information becomes available to suggest that MRI may not be safe for pregnant women or their fetuses we will inform the subjects of such information.

**8.3 Blood draw risk:** Commonly, there may be discomfort or pain at the site at the time of venipuncture, or bleeding or bruising post-venipuncture. Uncommonly, there is a very small risk of infection, which can be treated. Participants will be asked to contact their PCP and the study PI in the event of any adverse outcome.

**8.4 Minimizing risk of Breach of Data Security and Privacy:** Data obtained from human subjects will be

confidential and accessed only by members of the study team with appropriate IRB and HIPAA training, as assured by standard training protocols at VUMC. Data is maintained and secured in locked file cabinets or on encrypted, password protected computers, located in locked offices, and following Health Insurance Portability and Accountability Act (HIPAA) guidelines and the policies and procedures of VU and VUMC. Individuals will be identified by a numerical code that will be kept separate from study data.

## **9.0 REPORTING OF ADVERSE EVENTS OR UNANTICIPATED PROBLEMS INVOLVING RISK TO PARTICIPANTS OR OTHERS**

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We define an adverse event as any adverse change in health or development of a side effect occurring in a study participant after enrollment. These may be expected events (known drug effects, as detailed in the consent form, safety monitoring plan, or package insert) or unexpected events. The PI and Co-investigators will review any AE's that occurred during a participant's study experience, and determine their magnitude and causal attribution using the scale below. Every six months the PI and Co-investigators will review the magnitude and frequency of AE's and report such information to the IRB.

AE's of grade three or higher in the scale below will be reported immediately to the IRB using the Report of Adverse Events form and to the Program Director of the appropriate funding agency. In conjunction with the IRB, the PI then will determine if modifications to the protocol are warranted.

The primary method for ensuring data accuracy and protocol compliance will be the involvement of the PI in all aspects of the project. The PI and IRB have the authority to stop or modify the study at any time. During the semi-annual reviews, the PI and IRB will together decide if the study should continue unchanged, be modified, or closed to further enrollment.

Scaling of Adverse Events: Attribution of Cause:

- a. Definite: Adverse event (AE) will clearly be related to investigational agents or other intervention.
- b. Probable: AE will likely be related to investigational agents or other intervention.
- c. Possible: AE may be related to investigational agents or other intervention.
- d. Not Likely: AE will doubtfully be related to investigational agents or other intervention.
- e. Unrelated: AE will clearly not be related to investigational agents or other intervention.

Grading of Severity

0: No AE or within normal limits.

1: Mild AE.

2: Moderate AE.

3: Severe AE resulting in inpatient hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

4: Life-threatening or disabling AE.

5: Fatal AE

## **10.0 STUDY WITHDRAWAL/DISCONTINUATION**

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Subjects will be withdrawn from the study for safety considerations, non-compliance with study procedures, difficulties with scheduling or participation, excess movement or anxiety during scanning, or other reasons that the PI or study coordinators conclude will impair the scientific utility of the study. Subjects will be provided an explanation by the investigator if they are withdrawn from the study. In addition, subjects can voluntarily withdraw from the study at any time.

## **11.0 STATISTICAL CONSIDERATIONS**

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**11.1 Data Management:** All study data will be stored in a REDCap study database. The exception is for the raw and processed MRI scans that will be stored in the Vanderbilt XNAT Image Database system.

## 11.2 Statistical Analyses:

**11.2.a. Drug levels:** We will collect serum drug levels at the time of imaging to create a dose-response curve. The response will be defined as the change of a specific measure (hippocampal activity) from baseline. We will utilize nonlinear regression methods to create curves. Many studies have established a dose-response curve for epilepsy efficacy and safety (Boon et al., 2002; Meencke and Buyle, 2006; Rhee et al., 2017), but no dose-response curve currently exists for other measures such as imaging markers.

**11.2.b. Clinical Data:** The data will be analyzed both within and across diagnostic groups (patient, healthy control) and time-points (baseline assessment, after LEV intervention). Analyses of variance and linear mixed models will be used to compare group scores and the strength of the relation between neurocognitive and imaging outcome measures.

**11.2.c. Neurocognitive Data:** The data will be analyzed both within and across diagnostic groups (patient, healthy control) and time-points (baseline assessment, after LEV intervention). Analyses of variance and linear mixed models will be used to compare group scores.

**11.2.d. Imaging Data:** All images will be converted to an analyzable format. Spatial preprocessing will be performed using SPM5 (Functional Imaging Laboratory, London, UK) and FSL software (Analysis Group, FMRIB, Oxford, UK) or other comparable software. This will allow for realignment and transformation into a standardized space. Pairwise subtractions will then be performed, yielding images of mean difference and standard deviation, which can be used to produce z-scores and statistical parametric maps (SPMs). Statistical parametric maps will be constructed using a mixed effects model (subjects are considered random effects, conditions are considered fixed effects). SPM or other comparable software will allow us to test for condition effects, group effects, and group-by-condition interactions. Duration of illness and treatment will be assessed as confounding variables using an analysis of covariance. The duration of illness will be added into the fixed effects statistical model for the within group analysis as a covariate. Alternative methods will be employed when the data suggest a more appropriate method. The effects of duration of illness and treatment on structural imaging data will be assessed by correlation analysis.

**11.3 Power:** We calculated power for our primary aim of modulation of hippocampal activity based on a similar study that detected changes in hippocampal activation between healthy controls and a group of aMCI patients receiving two weeks of oral LEV (Bakker et al., 2012). Using the effect sizes demonstrated in this paper, at N = 40 (healthy control sample N = 20; psychosis patient sample N = 20) and alpha = 0.05, we will have 80.3% power to detect a change in hippocampal activity.

## 12.0 PRIVACY/CONFIDENTIALITY ISSUES

The data files generated by the MRI scanner are coded using a project name and unique number generated sequentially. The scanner technicians will not have access to the key for this information. Image analysis will use the coded files. The safety surveys described above include questions about sensitive health issues. This information will remain with the signed consent form in a secured area near the scanner. Electronic databases containing identifiable subject information will be password encoded. Written information containing subject identifiers (informed consent, lab results, interview questionnaires, subject payment, etc.) will be stored in file cabinets in offices within the departments of Radiology and Psychiatry. Subjects will be assigned an alphanumeric code that will be used to label all research data including all questionnaires and MRI data.



### 13.0 FOLLOW-UP AND RECORD RETENTION

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We anticipate participant recruitment and contact with subjects to be completed within one month. Study records will be maintained for at least two years after the study is closed with the IRB. In accordance with Vanderbilt guidelines, and as outlined to the subjects in the consent form, the subjects' confidentiality will be ensured throughout the study. Image data will be acquired by the 3 Tesla scanner and will be stored both on digital media (which will not leave the secured scanner area) and on Vanderbilt's secure REDCap database. The data may be maintained for an indefinite period of time since scientific progress may indicate that new analyses be carried out on previously obtained data. Future studies/analyses will be carried out with approval of the IRB. If paper records are to be destroyed those containing subject identifiers will be shredded directly or transferred to the hospital's shredding service. If electronic data containing subject identifiers is to be destroyed it will be disposed of using a medium-appropriate destruction method to prevent recovery. Data not containing subject identifiers will be disposed of by any convenient method.

In compliance with the National Institute of Health data sharing initiative, imaging data without any personal information attached may be shared with other investigators or public data repositories, which provides the research community with open access to datasets contributed by labs around the world. Information will be completely anonymized with demographics limited to age (accurate to the year up to 90 years old, or "90+" for older individuals), gender (male, female), group membership (e.g., disease/treatment state) and handedness. Data will be transferred using secure file transfer protocols.

### 14.0 REFERENCES

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- Association, A.P., 2016. Diagnostic and Statistical Manual of Mental Disorders, BMC Med. <https://doi.org/10.1176/appi.books.9780890425596.744053>
- Bakker, A., Albert, M.S., Krauss, G., Speck, C.L., Gallagher, M., 2015. Response of the medial temporal lobe network in amnesic mild cognitive impairment to therapeutic intervention assessed by fMRI and memory task performance. *NeuroImage Clin.* 7, 688–698. <https://doi.org/10.1016/j.nicl.2015.02.009>
- Bakker, A., Krauss, G.L., Albert, M.S., Speck, C.L., Jones, L.R., Stark, C.E., Yassa, M.A., Bassett, S.S., Shelton, A.L., Gallagher, M., 2012. Reduction of Hippocampal Hyperactivity Improves Cognition in Amnesic Mild Cognitive Impairment. *Neuron* 74, 467–474. <https://doi.org/10.1016/j.neuron.2012.03.023>
- Ben-Menachem, E., Falter, U., 2000. Efficacy and tolerability of levetiracetam 3000 mg/d in patients with refractory partial seizures: A multicenter, double-blind, responder-selected study evaluating monotherapy. *Epilepsia* 41, 1276–1283. <https://doi.org/10.1111/j.1528-1157.2000.tb04605.x>
- Benes, F.M., 1999. Evidence for altered trisynaptic circuitry in schizophrenic hippocampus. *Biol. Psychiatry* 46, 589–599. [https://doi.org/10.1016/S0006-3223\(99\)00136-5](https://doi.org/10.1016/S0006-3223(99)00136-5)
- Besag, F.M.C., Berry, D., 2006. Interactions between antiepileptic and antipsychotic drugs. *Drug Saf.* 29, 95–118. <https://doi.org/10.2165/00002018-200629020-00001>
- Boon, P., Chauvel, P., Pohlmann-Eden, B., Otoul, C., Wroe, S., 2002. Dose-response effect of levetiracetam 1000 and 2000 mg/day in partial epilepsy. *Epilepsy Res.* 48, 77–89. [https://doi.org/10.1016/S0920-1211\(01\)00323-0](https://doi.org/10.1016/S0920-1211(01)00323-0)
- Cereghino, J.J., Biton, V., Abou-Khalil, B., Dreifuss, F., Gauer, L.J., Leppik, I., Abou-Khalil, B., Bashuk, R., Beydoun, A., Biton, V., Bromfield, E., Browne, T.R., Celesia, G.G., Cereghino, J., Dean, J.C., Dengler, J., Dreifuss, F.E., Ferrendelli, J.A., Granner, M., Harden, C., Harvey, J., Hier, D.B., Hoch, D., Mutton, J.T., Iyer, V.G., Jacobson, M., King, J.A., Kirby, L.C., Lebow, S.S., Leppik, I.E., Locke, G., Matsuo, F., Newsom, M., Penovich, P., Radtke, R.A., Ramani, V., Remler, M.P., Rowan, A.J., Ruggles, K., Singer, R.P., Treiman, D.M., Michael, M., Wcstbrook, E., Willmore, L.J., Wilner, A., 2000. Levetiracetam for partial seizures: Results of a double-blind, randomized clinical trial. *Neurology* 55, 236–242. <https://doi.org/10.1212/WNL.55.2.236>
- Cramer, J.A., Smith, D.B., Mattson, R.H., Escueta, A.V.D., Collins, J.F., Browne, T.R., Crill, W.E., Homan, R.W., Mayersdorf, A., McCutchen, C.B., McNamara, J.O., Rosenthal, N.P., Treiman, D.M., Wilder, B.J., Williamson, P.D., 1983. A method of quantification for the evaluation of antiepileptic drug therapy.

- Neurology 33, 26–37.
- Devi, L., Ohno, M., 2013. Effects of levetiracetam, an antiepileptic drug, on memory impairments associated with aging and Alzheimer's disease in mice. *Neurobiol. Learn. Mem.* 102, 7–11. <https://doi.org/10.1016/j.nlm.2013.02.001>
- Dooley, M., Plosker, G.L., 2000. Levetiracetam: A review of its adjunctive use in the management of partial onset seizures. *Drugs* 60, 871–893. <https://doi.org/10.2165/00003495-200060040-00004>
- First, M.B., 2015. Structured Clinical Interview for the DSM (SCID). *Encycl. Clin. Psychol.* 1–6. <https://doi.org/10.1002/9781118625392.wbecp351>
- Freund, T.F., 2003. Interneuron Diversity series: Rhythm and mood in perisomatic inhibition. *Trends Neurosci.* 26, 489–495. [https://doi.org/10.1016/S0166-2236\(03\)00227-3](https://doi.org/10.1016/S0166-2236(03)00227-3)
- Friston, K.J., Liddle, P.F., Frith, C.D., Hirsch, S.R., Frackowiak, R.S.J., 1992. The left medial temporal region and schizophrenia: A pet study. *Brain* 115, 367–382. <https://doi.org/10.1093/brain/115.2.367>
- Gambardella, A., Labate, A., Colosimo, E., Ambrosio, R., Quattrone, A., 2008. Monotherapy for partial epilepsy: Focus on levetiracetam. *Neuropsychiatr. Dis. Treat.* 4, 33–38. <https://doi.org/10.2147/ndt.s1655>
- Gill, K., Grace, A., 2014. The Role of  $\gamma$ -GABA<sub>A</sub> Receptor Agonists in the Treatment of Cognitive Deficits in Schizophrenia. *Curr. Pharm. Des.* 20, 5069–5076. <https://doi.org/10.2174/1381612819666131216114612>
- Gomes, F. V., Rincón-Cortés, M., Grace, A.A., 2016. Adolescence as a period of vulnerability and intervention in schizophrenia: Insights from the MAM model. *Neurosci. Biobehav. Rev.* 70, 260–270. <https://doi.org/10.1016/j.neubiorev.2016.05.030>
- Gozzi, A., Crestan, V., Turrini, G., Clemens, M., Bifone, A., 2010. Antagonism at serotonin 5-HT<sub>2A</sub> receptors modulates functional activity of frontohippocampal circuit. *Psychopharmacology (Berl.)* 209, 37–50. <https://doi.org/10.1007/s00213-009-1772-4>
- Gozzi, A., Herdon, H., Schwarz, A., Bertani, S., Crestan, V., Turrini, G., Bifone, A., 2008. Pharmacological stimulation of NMDA receptors via co-agonist site suppresses fMRI response to phencyclidine in the rat. *Psychopharmacology (Berl.)* 201, 273–284. <https://doi.org/10.1007/s00213-008-1271-z>
- Gur, R.E., Mozley, P.D., Resnick, S.M., Mozley, L.H., Shtasel, D.L., Gallacher, F., Arnold, S.E., Karp, J.S., Alavi, A., Reivich, M., Gur, R.C., 1995. Resting Cerebral Glucose Metabolism in First-Episode and Previously Treated Patients with Schizophrenia Relates to Clinical Features. *Arch. Gen. Psychiatry* 52, 657–667. <https://doi.org/10.1001/archpsyc.1995.03950200047013>
- Hall, A.M., Throesch, B.T., Buckingham, S.C., Markwardt, S.J., Peng, Y., Wang, Q., Hoffman, D.A., Roberson, E.D., 2015. Tau-dependent Kv4.2 depletion and dendritic hyperexcitability in a mouse model of Alzheimer's disease. *J. Neurosci.* 35, 6221–6230. <https://doi.org/10.1523/JNEUROSCI.2552-14.2015>
- Hamilton, M., 1960. A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry* 23, 56–62. <https://doi.org/10.1136/jnnp.23.1.56>
- Hannula, D.E., Ranganath, C., Ramsay, I.S., Solomon, M., Yoon, J., Niendam, T.A., Carter, C.S., Ragland, J.D., 2010. Use of eye movement monitoring to examine item and relational memory in schizophrenia. *Biol. Psychiatry* 68, 610–616. <https://doi.org/10.1016/j.biopsych.2010.06.001>
- Heckers, S., Konradi, C., 2015. GABAergic mechanisms of hippocampal hyperactivity in schizophrenia. *Schizophr. Res.* 167, 4–11. <https://doi.org/10.1016/j.schres.2014.09.041>
- Ji-Qun, C., Ishihara, K., Nagayama, T., Serikawa, T., Sasa, M., 2005. Long-lasting antiepileptic effects of levetiracetam against epileptic seizures in the spontaneously epileptic rat (SER): Differentiation of levetiracetam from conventional antiepileptic drugs. *Epilepsia* 46, 1362–1370. <https://doi.org/10.1111/j.1528-1167.2005.29604.x>
- Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr. Bull.* 13, 261–276. <https://doi.org/10.1093/schbul/13.2.261>
- Klausberger, T., Somogyi, P., 2008. Neuronal diversity and temporal dynamics: The unity of hippocampal circuit operations. *Science (80-. )*. <https://doi.org/10.1126/science.1149381>
- Koh, M.T., Haberman, R.P., Foti, S., McCown, T.J., Gallagher, M., 2010. Treatment strategies targeting excess hippocampal activity benefit aged rats with cognitive impairment. *Neuropsychopharmacology* 35, 1016–1025. <https://doi.org/10.1038/npp.2009.207>

- Koh, M.T., Shao, Y., Rosenzweig-Lipson, S., Gallagher, M., 2018. Treatment with levetiracetam improves cognition in a ketamine rat model of schizophrenia. *Schizophr. Res.* 193, 119–125. <https://doi.org/10.1016/j.schres.2017.06.027>
- Kossoff, E.H., Bergey, G.K., Freeman, J.M., Vining, E.P.G., 2001. Levetiracetam psychosis in children with epilepsy. *Epilepsia* 42, 1611–1613. <https://doi.org/10.1046/j.1528-1157.2001.32101.x>
- Krasowski, M.D., 2010. Therapeutic Drug Monitoring of the Newer Anti-Epilepsy Medications. *Pharmaceuticals* 3, 1909–1935. <https://doi.org/10.3390/ph3061909>
- Lehman, A.F., Lieberman, J.A., Dixon, L.B., McGlashan, T.H., Miller, A.L., Perkins, D.O., Kreyenbuhl, J., McIntyre, J.S., Charles, S.C., Altshuler, K., Cook, I., Cross, C.D., Mellman, L., Moench, L.A., Norquist, G., Twemlow, S.W., Woods, S., Yager, J., Gray, S.H., Askland, K., Pandya, R., Prasad, K., Johnston, R., Nininger, J., Peele, R., Anzia, D.J., Benson, R.S., Lurie, L., Walker, R.D., Kunkle, R., Simpson, A., Fochtmann, L.J., Hart, C., Regier, D., 2004. Practice Guideline for the Treatment of Patients with Schizophrenia, Second Edition. *Am. J. Psychiatry* 161. <https://doi.org/10.1176/appi.books.9780890423363.45859>
- Liddle, P.F., Friston, K.J., Frith, C.D., Hirsch, S.R., Jones, T., Frackowiak, R.S.J., 1992. Patterns of cerebral blood flow in schizophrenia. *Br. J. Psychiatry* 160, 179–186. <https://doi.org/10.1192/bjp.160.2.179>
- Lodge, D.J., Behrens, M.M., Grace, A.A., 2009. A Loss of Parvalbumin-Containing Interneurons Is Associated with Diminished Oscillatory Activity in an Animal Model of Schizophrenia. *J. Neurosci.* <https://doi.org/10.1523/JNEUROSCI.5419-08.2009>
- Logothetis, N.K., 2008. What we can do and what we cannot do with fMRI. *Nature* 453, 869–878. <https://doi.org/10.1038/nature06976>
- Lynch, B.A., Lambeng, N., Nocka, K., Kensel-Hammes, P., Bajjalieh, S.M., Matagne, A., Fuks, B., 2004. The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. *Proc. Natl. Acad. Sci. U. S. A.* 101, 9861–9866. <https://doi.org/10.1073/pnas.0308208101>
- Lyseng-Williamson, K.A., 2011. Levetiracetam: A review of its use in epilepsy. *Drugs* 71, 489–514. <https://doi.org/10.2165/11204490-000000000-00000>
- McHugo, M., Talati, P., Armstrong, K., Vandekar, S.N., Blackford, J.U., Woodward, N.D., Heckers, S., 2019. Hyperactivity and Reduced Activation of Anterior Hippocampus in Early Psychosis. *Am. J. Psychiatry* *appi.ajp.2019.1*. <https://doi.org/10.1176/appi.ajp.2019.19020151>
- Meencke, H.J., Buyle, S., 2006. Assessment of a dose-response relationship of levetiracetam. *Eur. J. Neurol.* 13, 942–946. <https://doi.org/10.1111/j.1468-1331.2006.01381.x>
- Modinos, G., Şimşek, F., Azis, M., Bossong, M., Bonoldi, I., Samson, C., Quinn, B., Perez, J., Broome, M.R., Zelaya, F., Lythgoe, D.J., Howes, O.D., Stone, J.M., Grace, A.A., Allen, P., McGuire, P., 2018. Prefrontal GABA levels, hippocampal resting perfusion and the risk of psychosis. *Neuropsychopharmacology* 43, 2652–2659. <https://doi.org/10.1038/s41386-017-0004-6>
- Morisky, D.E., Green, L.W., Levine, D.M., 1986. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med. Care* 24, 67–74. <https://doi.org/10.1097/00005650-198601000-00007>
- Morosini, P.L., Magliano, L., Brambilla, L., Ugolini, S., Pioli, R., 2000. Development, reliability and acceptability of a new version of the DSM- IV Social Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatr. Scand.* 101, 323–329. <https://doi.org/10.1034/j.1600-0447.2000.101004323.x>
- Mula, M., Trimble, M.R., Yuen, A., Liu, R.S.N., Sander, J.W.A.S., 2003. Psychiatric adverse events during levetiracetam therapy. *Neurology* 61, 704–706. <https://doi.org/10.1212/01.WNL.0000078031.32904.0D>
- Neyens, L.G.J., Alpherts, W.C.J., Aldenkamp, A.P., 1995. Cognitive effects of a new pyrrolidine derivative (levetiracetam) in patients with epilepsy. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 19, 411–419. [https://doi.org/10.1016/0278-5846\(95\)00022-N](https://doi.org/10.1016/0278-5846(95)00022-N)
- Nicolas, J.M., Collart, P., Gerin, B., Mather, G., Trager, W., Levy, R., Roba, J., 1999. In vitro evaluation of potential drug interactions with levetiracetam, a new antiepileptic agent. *Drug Metab. Dispos.* 27, 250–254.
- Olbrich, H.G., Braak, H., 1985. Ratio of pyramidal cells versus non-pyramidal cells in sector CA1 of the human Ammon's horn. *Anat. Embryol. (Berl.)* 173, 105–110. <https://doi.org/10.1007/BF00707308>

- Olincy, A., Stevens, K.E., 2007. Treating schizophrenia symptoms with an  $\alpha 7$  nicotinic agonist, from mice to men. *Biochem. Pharmacol.* 74, 1192–1201. <https://doi.org/10.1016/j.bcp.2007.07.015>
- Patsalos, P.N., 2004. Clinical pharmacokinetics of levetiracetam. *Clin. Pharmacokinet.* 43, 707–724. <https://doi.org/10.2165/00003088-200443110-00002>
- Patsalos, P.N., 2000. Pharmacokinetic profile of levetiracetam toward ideal characteristics. *Pharmacol. Ther.* 85, 77–85. [https://doi.org/10.1016/S0163-7258\(99\)00052-2](https://doi.org/10.1016/S0163-7258(99)00052-2)
- Peralta, V., Cuesta, M.J., 1994. Psychometric properties of the Positive and Negative Syndrome Scale (PANSS) in schizophrenia. *Psychiatry Res.* 53, 31–40. [https://doi.org/10.1016/0165-1781\(94\)90093-0](https://doi.org/10.1016/0165-1781(94)90093-0)
- Perez, S.M., Lodge, D.J., 2014. New approaches to the management of schizophrenia: Focus on aberrant hippocampal drive of dopamine pathways. *Drug Des. Devel. Ther.* 8, 887–896. <https://doi.org/10.2147/DDDT.S42708>
- Perucca, P., Gilliam, F.G., 2012. Adverse effects of antiepileptic drugs. *Lancet Neurol.* 11, 792–802. [https://doi.org/10.1016/S1474-4422\(12\)70153-9](https://doi.org/10.1016/S1474-4422(12)70153-9)
- Potter, D., Summerfelt, A., Gold, J., Buchanan, R.W., 2006. Review of clinical correlates of P50 sensory gating abnormalities in patients with schizophrenia. *Schizophr. Bull.* 32, 692–700. <https://doi.org/10.1093/schbul/sbj050>
- Rhee, S. jin, Shin, J.W., Lee, S.H., Moon, J., Kim, T.J., Jung, K.Y., Park, K. Il, Lee, S.T., Jung, K.H., Yu, K.S., Jang, I.J., Chu, K., Lee, S.K., 2017. Population pharmacokinetics and dose-response relationship of levetiracetam in adult patients with epilepsy. *Epilepsy Res.* 132, 8–14. <https://doi.org/10.1016/j.eplepsyres.2017.02.011>
- Rossetti, A.O., Bromfield, E.B., 2005. Levetiracetam in the treatment of status epilepticus in adults: A study of 13 episodes. *Eur. Neurol.* 54, 34–38. <https://doi.org/10.1159/000087385>
- Saha, S., Chant, D., Welham, J., McGrath, J., 2005. A systematic review of the prevalence of schizophrenia. *PLoS Med.* 2, 0413–0433. <https://doi.org/10.1371/journal.pmed.0020141>
- Sanchez, P.E., Zhu, L., Verret, L., Vossel, K.A., Orr, A.G., Cirrito, J.R., Devidze, N., Ho, K., Yu, G.Q., Palop, J.J., Mucke, L., 2012. Levetiracetam suppresses neuronal network dysfunction and reverses synaptic and cognitive deficits in an Alzheimer's disease model. *Proc. Natl. Acad. Sci. U. S. A.* 109. <https://doi.org/10.1073/pnas.1121081109>
- Schobel, S.A., Chaudhury, N.H., Khan, U.A., Paniagua, B., Styner, M.A., Asllani, I., Inbar, B.P., Corcoran, C.M., Lieberman, J.A., Moore, H., Small, S.A., 2013. Imaging Patients with Psychosis and a Mouse Model Establishes a Spreading Pattern of Hippocampal Dysfunction and Implicates Glutamate as a Driver. *Neuron* 78, 81–93. <https://doi.org/10.1016/j.neuron.2013.02.011>
- Schobel, S.A., Lewandowski, N.M., Corcoran, C.M., Moore, H., Brown, T., Malaspina, D., Small, S.A., 2009. Differential targeting of the CA1 subfield of the hippocampal formation by schizophrenia and related psychotic disorders. *Arch. Gen. Psychiatry* 66, 938–946. <https://doi.org/10.1001/archgenpsychiatry.2009.115>
- Shorvon, S.D., Löwenthal, A., Janz, D., Bielen, E., Loiseau, P., 2000. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. *Epilepsia* 41, 1179–1186. <https://doi.org/10.1111/j.1528-1157.2000.tb00323.x>
- Smucny, J., Stevens, K.E., Tregellas, J.R., 2015. The antiepileptic drug levetiracetam improves auditory gating in DBA/2 mice. *npj Schizophr.* 1. <https://doi.org/10.1038/npjpsz.2015.2>
- Smucny, J., Tregellas, J.R., 2017. Targeting neuronal dysfunction in schizophrenia with nicotine: Evidence from neurophysiology to neuroimaging. *J. Psychopharmacol.* 31, 801–811. <https://doi.org/10.1177/0269881117705071>
- Stan, A.D., Ghose, S., Zhao, C., Hulsey, K., Mihalakos, P., Yanagi, M., Morris, S.U., Bartko, J.J., Choi, C., Tamminga, C.A., 2015. Magnetic resonance spectroscopy and tissue protein concentrations together suggest lower glutamate signaling in dentate gyrus in schizophrenia. *Mol. Psychiatry* 20, 433–439. <https://doi.org/10.1038/mp.2014.54>
- Stevens, K.E., Wear, K.D., 1997. Normalizing effects of nicotine and a novel nicotinic agonist on hippocampal auditory gating in two animal models. *Pharmacol. Biochem. Behav.* 57, 869–874. [https://doi.org/10.1016/S0091-3057\(96\)00466-2](https://doi.org/10.1016/S0091-3057(96)00466-2)

- Stratton, S.C., Large, C.H., Cox, B., Davies, G., Hagan, R.M., 2003. Effects of lamotrigine and levetiracetam on seizure development in a rat amygdala kindling model. *Epilepsy Res.* 53, 95–106. [https://doi.org/10.1016/S0920-1211\(02\)00254-1](https://doi.org/10.1016/S0920-1211(02)00254-1)
- Stretton, J., Winston, G., Sidhu, M., Centeno, M., Vollmar, C., Bonelli, S., Symms, M., Koepp, M., Duncan, J.S., Thompson, P.J., 2012. Neural correlates of working memory in Temporal Lobe Epilepsy - An fMRI study. *Neuroimage* 60, 1696–1703. <https://doi.org/10.1016/j.neuroimage.2012.01.126>
- Suberbielle, E., Sanchez, P.E., Kravitz, A. V., Wang, X., Ho, K., Eilertson, K., Devidze, N., Kreitzer, A.C., Mucke, L., 2013. Physiologic brain activity causes DNA double-strand breaks in neurons, with exacerbation by amyloid- $\beta$ . *Nat. Neurosci.* 16, 613–621. <https://doi.org/10.1038/nn.3356>
- Talati, P., Rane, S., Kose, S., Blackford, J.U., Gore, J., Donahue, M.J., Heckers, S., 2014. Increased hippocampal CA1 cerebral blood volume in schizophrenia. *NeuroImage Clin.* 5, 359–364. <https://doi.org/10.1016/j.nicl.2014.07.004>
- Tregellas, J.R., 2014. Neuroimaging biomarkers for early drug development in schizophrenia. *Biol. Psychiatry* 76, 111–119. <https://doi.org/10.1016/j.biopsych.2013.08.025>
- Uhlhaas, P.J., 2013. Dysconnectivity, large-scale networks and neuronal dynamics in schizophrenia. *Curr. Opin. Neurobiol.* 23, 283–290. <https://doi.org/10.1016/j.conb.2012.11.004>
- Verrotti, A., Prezioso, G., Di Sabatino, F., Franco, V., Chiarelli, F., Zaccara, G., 2015. The adverse event profile of levetiracetam: A meta-analysis on children and adults. *Seizure* 31, 49–55. <https://doi.org/10.1016/j.seizure.2015.07.004>
- Wandschneider, B., Stretton, J., Sidhu, M., Centeno, M., Kozák, L.R., Symms, M., Thompson, P.J., Duncan, J.S., Koepp, M.J., 2014. Levetiracetam reduces abnormal network activations in temporal lobe epilepsy. *Neurology* 83, 1508–1512. <https://doi.org/10.1212/WNL.0000000000000910>
- Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: Reliability, validity and sensitivity. *Br. J. Psychiatry* 133, 429–435. <https://doi.org/10.1192/bjp.133.5.429>
- Zhang, Q., Yang, F., Hu, Z., Xu, Q., Bernhardt, B.C., Quan, W., Li, Q., Zhang, Z., Lu, G., 2018. Antiepileptic drug of levetiracetam decreases centrottemporal spike-associated activation in rolandic epilepsy. *Front. Neurosci.* 12. <https://doi.org/10.3389/fnins.2018.00796>
- Zhang, Q., Yang, F., Hu, Z., Zhang, Z., Xu, Q., Dante, M., Wu, H., Li, Z., Li, Q., Li, K., Lu, G., 2017. Resting-state fMRI revealed different brain activities responding to valproic acid and levetiracetam in benign epilepsy with central-temporal spikes. *Eur. Radiol.* 27, 2137–2145. <https://doi.org/10.1007/s00330-016-4531-z>
- Zou, L.P., Ding, C.H., Song, Z.J., Li, X.F., 2012. Stevens-Johnson syndrome induced by levetiracetam. *Seizure* 21, 823–825. <https://doi.org/10.1016/j.seizure.2012.09.005>

