# Comparing Therapeutic Efficacy and Cognitive Side Effects of ECT Using Ketamine versus Methohexital Anesthesia
# (With MRI Addendum)

## Rationale

Despite major advances in the treatment of mood disorders, depression remains a serious public health problem. In a recently published Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, patients had remission rates of 37%, 31%, 14% and 13% for four distinct types of pharmacotherapy treatment.[1] Another limitation to pharmacological treatment is the delayed response, which can often take up to several weeks and is especially deleterious for suicidal patients. For these reasons, electroconvulsive therapy (ECT) represents an important and efficacious treatment modality for the treatment of depression. ECT generally provides faster amelioration of depressive symptoms and its efficacy is reported to be 65 to 85%[2] . However, even with ECT some patients do not respond and the antidepressant response requires multiple sessions increasing risk of impaired cognitive function, which still remains the limiting factor in its use.

Ketamine is a non-barbiturate anesthetic that has been used infrequently as an anesthetic in ECT. As ketamine has no anticonvulsant properties as barbiturate anesthetics do, its use has been generally reserved for instances when a seizure cannot be elicited from a patient despite the application of maximum device settings.[3] However, there are recent reports that demonstrate ketamine's favorable seizure and cognitive profile.[4]

Furthermore, ketamine is hypothesized to possess intrinsic antidepressant properties when used as monotherapy for depression. Several investigators have determined that ketamine, at sub-anesthetic doses, alleviates depressive symptoms in animals. There is some recent evidence that the use of ketamine in ECT may enhance the overall outcome. A non-randomized trial by Okamoto[6] shows a faster response when ECT is given with ketamine anesthesia compared to that with propofol. We propose a pilot study to measure both therapeutic efficacy and cognitive side effects of ECT using ketamine compared to methohexital in depressed patients.

Although electroconvulsive therapy (ECT), regardless of the anesthetic agent, is a highly effective form of treatment in major depression, very little is known about the underlying mechanism of action[7]. Neuroimaging is a non-invasive technique which may provide more insight into the underlying changes in the neurophysiologic circuitry. Several PET investigations

have examined regional changes in blood flow or glucose consumption before and after ECT[8-11]. However, the results of these studies were sometimes contradictory and this type of methodology was not suited to detect possible changes in brain networks. In this last decade novel fMRI techniques[12] have became available to measure and evaluate networks in the brain. Hence, in this pilot study, we will also collect longitudinal MRI data (once before ECT and twice after ECT) to gain novel insight into the effect of ECT at a deeper level.

In addition, we will also explore other parameters of ECT, such as seizure duration and morphology as well as hemodynamic and behavioral changes when using ketamine versus methohexital for ECT.

## Specific Aims

### Primary Aims

To compare the efficacy of ECT with ketamine anesthesia to that with methohexital for depressed patients undergoing an acute course of standard ECT treatment as defined by the time needed to achieve remission. We will also characterize the temporal pattern of improvement in depression between the two treatment groups.

### Primary outcome

The primary outcome will be the time to achieve remission. Remission is defined as two consecutive $HRSD_{24}$ scores < 10, and $HRSD_{24}$ total score does not increase > 3 points on the second consecutive $HRSD_{24}$, or remains < 6 at the last two consecutive treatments. HRSD-24 scores are used to define remission.

### Secondary Aim A

To compare the cognitive side effects of ECT when used with ketamine to that with methohexital

### Secondary Aim B

To use resting state and task related fMRI to identify ECT related functional network changes in the brain. Using resting state fMRI before and after ECT, we will (a) identify networks modulated by ECT (defined as a decrease or increase in functional connectivity from baseline to follow up scans), and we will (b) follow up their expression in the upcoming weeks, we will (c) identify functional networks of the brain which are correlated with superior clinical ECT outcome and we will (d) identify functional networks of the brain which are correlated with side effect profiles.

### Secondary Outcome

To determine the cognitive side effects we will use the following neuropsychological battery:

- Mini- Mental State Examination (MMSE),
- Postictal Recovery of Orientation,
- Rey Auditory Verbal Learning Test (RAVLT)

- Autobiographical Memory Interview – Short Form (AMI – SF),
- Subjective Memory Questionnaire (SMQ),
- Reading subtest of the Wide Range Achievement Test, 3rd Edition (WRAT-3)
- The Stroop Color Word Test (SCWT) (Golden version)
- Trail Making Test Part A & B
- Wechsler Adult Intelligence Test-Third Edition (WAIS-III), Digit Span Subtest
- WAIS-III Digit Symbol
- Controlled Oral Word Association Test (COWAT)
- N-Back

## Exploratory Aims

To compare other parameters of ECT when used with ketamine anesthesia to that with methohexital anesthesia. These parameters are:

1. Seizure duration.
2. Seizure morphology.
3. Hemodynamic changes during ECT procedure.
4. Postictal behavioral complications such as agitation or psychosis.
5. To detect differences in brain activation.

## Hypothesis

We hypothesize that patients who receive ketamine anesthesia during ECT will need fewer treatments to achieve remission. At the end of the ECT course they will display fewer cognitive side effects compared to those treated with methohexital anesthesia.

In the imaging part of this study, the main theoretical question is whether ECT exerts its effect primarily by altering networks. Our specific hypothesis is that ECT will decrease functional connectivity in the Default Mode Network.

## Background

A brief review of literature is presented relative to ketamine and:

1) Mechanism of action
2) Safety
3) Advantages for ECT

In addition a summary of the rationale behind the neuroimaging part of this study will be provided:

4) Neuroimaging studies in depression
5) Neuroimaging studies in ECT

### 1. Mechanism of action

Ketamine exerts its pharmacologic effects by binding noncompetitively to the N-methyl-D Aspartate (NMDA) receptor, a receptor that is physiologically activated by the excitatory neurotransmitters such as glutamate. This receptor is most densely located in the cerebral cortex and the hippocampus. Ketamine also binds weakly to the mu opioid receptor, a property that explains ketamine's analgesic actions. Finally, ketamine also binds weakly to monoamine transporters and can inhibit acetylocholinesterase.[13]

### 2. Safety

Both methohexital and ketamine are listed by the American Psychiatric Association Task Force Report as recommended anesthetic agents for ECT.[3] However, methohexital is an ultra short-acting barbiturate anesthetic that is currently the most commonly used agent during ECT. Traditionally, ketamine has not been used as a first-line agent in ECT because of its potential risk of causing psychotic-like symptoms, especially hallucinations. These properties have been demonstrated in a randomized, double-blind, placebo-controlled study by John Krystal.[13] In this study, 19 healthy patients experienced psychotic-like symptoms following 40-minute intravenous (IV) treatment of subanesthetic ketamine. Symptoms included perceptual effects, unusual thought content, illusions, and ideas of reference, paranoia, loose associations, tangentiality, concreteness, emotional withdrawal, blunted affect and psychomotor retardation. Thought disorder, dissociative symptoms and psychotic behavior in healthy volunteers treated with low-dose ketamine has also been observed by Adler et al and Morgan et al.[14;15]

However, a comprehensive literature search has shown that these adverse reactions from ketamine have rarely been observed with ECT.[3;4;16;17] A generally accepted explanation for this phenomenon is that ECT, through seizure depolarization, provides a brain protective mechanism by displacing ketamine from its binding site on the NMDA receptor.[4;18] This observation is supported by Mc Innes and James et al[17], Brewer et al[16], and Rasmussen et al [18], all of whom found insignificant adverse reactions following ECT with ketamine anesthesia. Although Andrew Krystal et al [4] describe a single incidence of hallucinations following treatment with ketamine anesthesia, the affected patient was unique in that he had the highest reported initial seizure threshold, had received the highest dose of ketamine (2.8mg/Kg) and had a history of significant alcohol abuse.

Theoretical adverse effects of ketamine in both anesthetic and sub-anesthetic doses include transient increases in blood pressure and pulse pressure as well as ataxia, nausea, dizziness, headache and confusion[18-21]. However, other investigators have reported that ketamine is well tolerated and that a transient increase in blood pressure is the only adverse effect associated with

ketamine. According to Rasmussen et al[18] ketamine use in ECT is both safe and well tolerated, with the only adverse effect being a transient increase in blood pressure that was successfully managed with beta blockers. Because of the increased cardiac work and myocardial oxygen consumption, ketamine use is not recommended in patients with severe coronary artery disease. It is also worth mentioning that ketamine has not been reported to increase post-operative confusion and in fact decreases post-operative depression as measured by depressed mood, suicidality and hypochondriasis.[22] Also, Brewer et al [16] noted an advantage of ketamine anesthesia on less respiratory depression. Overall, ketamine is a safe anesthetic for use during ECT and that there is no significant evidence of long term adverse reactions with its use.[4;13;23]

## 3. Advantages for ECT

When examining ketamine anesthesia specifically for ECT, there are three distinct advantages:

### a. Lowering seizure threshold

As previously mentioned, ketamine can allow for a therapeutic seizure in patients with a high seizure threshold[4]. Its use has been generally reserved for instances when a seizure cannot be elicited from a patient despite the application of maximum device settings.[3]

### b. Favorable cognitive side effects profile

Moderate impairment of short-term memory (STM) is a concerning side effect of ECT[3]. Several recent reports suggest that ketamine anesthesia may have a cognitive-sparing effect on memory function following ECT. The NMDA glutamate receptor mediates long-term changes in synaptic strength, i.e. long-term potentiation (LTP), responsible for memory formation. Antagonism of the NMDA receptor by ketamine may prevent the LTP-blocking hippocampal structural changes induced during a tonic-clonic seizure. This suggestion is rooted in animal studies indicating that ketamine prevents brain damage in the amygdala, piriform cortex and CA1 region of the hippocampus during status epilepticus, as well as protects from seizure-induced impairment of rat hippocampal LTP.

Krystal et al[4] demonstrated less cognitive side effects following ECT when patients were anesthetized with ketamine instead of methohexital. The primary measure of cognitive function was the extent of retrograde amnesia, the most common cognitive side effect of ECT. They also observed a more rapid cognitive recovery time after ECT in patients anesthetized with ketamine as opposed to methohexital. This is particularly notable because methohexital has a shorter duration of action than ketamine and it represents preliminary evidence that ketamine anesthesia may prevent STM loss after treatment.

McDaniel et al[23] noted improved memory function of a patient treated with ketamine anesthesia for ECT when compared with the same patient's previous ECT treatment using etomidate anesthesia. Hypothesizing that patients treated with ketamine anesthesia for ECT will have less

STM dysfunction than patients treated with etomidate anesthesia, McDaniel recruited ten patients with treatment resistant depression for a prospective trial. Each patient received six treatments, was treated with the same anesthetic throughout and there was no difference in remission rates between the two groups of patients. STM function was tested with a four-word recall similar to the STM item of the Mini Mental State Examination. McDaniel tested memory function after the anesthetics were completely excreted as to avoid impaired cognitive function due to the anesthetic itself. McDaniel discovered that ketamine-anesthetized patients had modest but statistically significant better memory function than etomidate-anesthetized patients. The difference in STM between the two groups reflects ketamine's memory-protective attribute, however, the mechanism by which ketamine prevents memory impairment is still unclear. It may be that ketamine prevents glutamate excitotoxicity, does not allow hippocampal remodeling or both.

### c. Antidepressant Effect

Ketamine may have an antidepressant effect in and of itself [24]. Arguably the most intriguing aspect of ketamine anesthesia for ECT is the fact that ketamine may have an intrinsic antidepressant effect. A striking case supporting this notion is described by Ostroff et al[25]. In this case, a patient with a 20-year history of pharmacotherapy-resistant depression and schizoaffective disorder inadvertently received anesthetic doses (0.5mg/kg) of ketamine alone during two failed ECT treatments. The patient reported an immediate improvement of her mood upon regaining consciousness after the first failed treatment, which continued up to the time of her second failed treatment. The patient reported a further improved mood after this second administration that lasted for 48 hours up to the time of her third treatment during which she experienced a successful ECT-induced seizure. After three more ECT treatments, the patient was in remission.

Similarly, Goforth et al [20] offer a case study of a patient with severe depression who received a IM injection of ketamine (1.5mg/kg) one hour prior to ECT. The patient immediately responded positively with a remission of depressive symptoms and he continued to improve over the next two days up to the time of his next scheduled ECT. The dramatic degree of improvement was unusual for a single ECT treatment, suggesting that anesthetic doses of ketamine prior to ECT enhance the antidepressant effect of the ECT session. Administering the anesthetic ketamine one hour before treatment ensured that the ECT-induced seizure depolarization would not displace ketamine from the NMDA receptor and confound the synergistic effect of ketamine with ECT.

An earlier study performed by Kudoh et al [22]does not involve ECT but provides evidence of the antidepressant effect of ketamine anesthesia in depressed patients. Here, anesthetic doses of ketamine improved post-operative depression in depressed patients undergoing orthopedic surgery. A small dose of ketamine anesthesia (1.0mg/kg) was used to induce anesthesia along with propofol and fentanyl whereas the control patients received only propofol and fentanyl. Since the ketamine-anesthetized patients experienced a significant reduction in postoperative

pain compared to control patients, and pain is closely related to the pathophysiology of depression, ketamine functioned not only as an analgesic but also as an antidepressant.

Ketamine had previously been observed to improve mood after adjunctive as well as inductive doses. Yilmaz[5] recognized that anesthetic doses of ketamine led to a long-term remittance of behavioral despair, an animal model of depression, in rats. The rats were subject to two forced swim tests, the second of which followed a single injection of saline or of anesthetic ketamine. The ketamine-injected animals immediately showed significantly less signs of behavioral despair (less immobility and more escape behaviors) for up to ten days compared to their control counterparts. This study suggests that ketamine may have a similar antidepressant effect in humans.

Furthermore, the significant mood-elevating effect of ketamine observed in Yilmaz's rats indicates that NMDA receptors and the glutaminergic system are involved in the pathophysiology of behavioral despair and depression. The prolonged effect of ketamine, particularly significant considering ketamine's short half-life of only two hours, may be due to a long-term change in glutamate activation. The brain areas most likely implicated in this long-term change are the frontal cortex, hippocampus and amygdala. These sites house learning and memory, and therefore, the learned helplessness displayed in the forced swim tests. It is also a possibility that ketamine's interaction at the NMDA receptor could affect mood and behavior through secondary effects on the monoaminergic and opiate systems. Similarly, ketamine has a weak affinity for the mu opiate receptor and a weak antagonism for a dopamine transporter.

These findings are consistent with several investigators, each of whom determined that sub-anesthetic, adjunctive doses of ketamine alleviate depression in humans. Berman et al[19] treated seven depressed patients with an infusion of either intravenous (IV) saline or IV ketamine (0.5mg/kg) on two occasions, one week apart. He concluded that a single dose of IV ketamine improved depressive symptoms within 72h. Zarate et al[21] performed a study almost identical in design to that of Berman, using a larger sample size of 18 patients with treatment resistant major depression. 71% of his ketamine-infused patients met response criteria for depression and 29% met remission criteria on the first day of the infusion. Zarate confirmed Berman's claim that a single dose of sub-anesthetic ketamine produces a noticeable antidepressant effect. Additionally, he detected the effect after only two hours and found that 35% of the patients maintained their response for one week afterwards. The time of onset and duration of relief of depressive symptoms was nearly identical for all patients. Both Berman and Zarate agreed that the lessening of the core depressive symptoms is distinct and temporally disconnected from the mild perceptual disturbances, cognitive deficits and ketamine "high" experienced by some patients in the hours immediately following infusion.

Corell et al[26] described two case studies of patients with treatment-resistant major depressive disorder who were infused for five days with sub-anesthetic ketamine. Although one of the two

patients required three cycles of ketamine infusions, both patients experienced rapid relief of their depressive symptoms following the infusion that lasted for months afterwards. The first patient experienced relief of her symptoms within 24 hours of beginning treatment. Positive improvement continued through the infusion and 12 months after the treatment, she remained in remission. The second patient noticed positive improvement 48 hours after the start of the infusion that lasted for 2.5 months at which point he required a second 5 day infusion treatment. After the second treatment, he noted improvement after 10 days that lasted for 6 months. After a third ketamine infusion, the patient remained in remission. Neither patient experienced any changes in liver function, blood pressure or pulse pressure although both patients experienced some light-headedness and feelings of inebriation during the course of the infusion.

In light of Berman, Zarate and Corell's[19,21;26] reports of an antidepressant response after a sub-anesthetic ketamine infusion Caric et al[24] treated a medication-resistant severely depressed patient with a small dose of IV ketamine (0.5 mg/kg). The patient experienced rapid improvement and began maintenance medication. When the patient relapsed after ten days, he was treated with a second ketamine infusion. This time, he continued maintenance medication but additionally began a series of ECT treatments, leading to a complete remission. This case illustrates the rapid relief of depressive symptoms following a ketamine infusion twice in the same patient. Furthermore, it indicates that the improvement cannot be maintained with medication alone but will be maintained with a combination of medication and ECT.

In conclusion, antidepressant medications take weeks to achieve therapeutic effect. Even after starting the medication, patients with severe depression continue to suffer with their symptoms and risk self harm. Furthermore, some patients experience severe depression that is resistant to pharmacotherapy. The fact that antidepressants are not universally effective combined with a lag period in their effectiveness indicates a significant limitation in their utility. For this reason, an alternate therapy that could provide rapid relief of depressive symptoms would have a profound impact on public health.

While ECT provides more immediate amelioration of depression, multiple treatments are still required to achieve remission. There remains an untapped potential to use anesthetic ketamine to augment ECT.

### Other advantages

Furthermore, ketamine anesthesia offers many advantages to the ECT patient. Ketamine can have analgesic effects that persist after the patient has emerged from anesthesia.[4,27] The ability of ketamine to be administered intramuscularly is useful in an agitated or aggressive patient. Also, ketamine can be an alternative anesthetic for patients with porphyria who should not be taking barbiturates or patients with lung disease who would benefit from an agent that offers less respiratory depression.[16; 18]

It is for these reasons that ketamine is being reexamined as a preferred anesthetic for ECT.

### Significance

Every year more than 100,000 patients in the United States and approximately 1,000,000 patients in the world receive ECT. According to the CORE group the average course of acute ECT for the treatment of a major depressive episode is 8 sessions.[2] The major limiting factor in the use of ECT is the cognitive side effects, which are cumulative in nature. If the use of ketamine were able to reduce the overall number of treatments to remission or be even minimally cognitive sparing, this will have a significant positive impact in the field. Examples of the positive effects are reducing the burden of illness on patients and their exposure to possible side effects of ECT. Also, reducing patients' length of hospitalization, and decreasing the cost of mental health care. It is for these reasons that ketamine is being reexamined as a preferred anesthetic for ECT.

### Future Directions

The results of the study will guide us to design bigger and definitive studies.

## 4. Neuroimaging studies in depression

In the 1930s and 40s, several observations suggested the existence of a system of brain structures that together are responsible for emotions. Kluver and Bucy discovered that large temporal lobe lesions in monkey led to a strange phenomenon in which the animal could not express fear in the presence of obviously fearful stimuli (psychic blindness). Papez and MacLean proposed that the Limbic System including the hippocampal formation, cingulate gyrus, and anterior thalamus regulates emotion and expression of emotion[28]. In the 1950s and 60s, tracing methods based on axonal degeneration began to clarify the connections of the structures of the limbic system. The cortical projections of the amygdala are widespread, but the strongest connections are with the mPFC, OFC, temporal pole, insula and hippocampus. Extensive projections exist to the nucleus accumbens and to the hypothalamus as well.[29] Recently a projection to the posterior cingulate cortex has been identified, which is particularly interesting, since this would be the last link to cover all of the classical regions of default mode network (DMN).[30] Neuroimaging measurements in Major Depressive Disorder (MDD) have consistently identified that subgenual PFC, a region part of the medial prefrontal region, has a pivotal role in the pathogenesis of depression. Drevets et al[31] found that this area has both lower perfusion and lower metabolism in depression. However later work by Mayberg et al. showed the opposite results. They showed that sadness and depression caused increased activation in subgenual PFC.[32] Although these findings appear to contradict each other the findings may be reconciled if activation is corrected for gray matter atrophy. Today it is widely accepted that if we correct for atrophy, the net effect is increased activation in this area. Recently published data also support the view that DMN and its regions are indeed affected in major depression.[33] The lack of deactivation of this network could

explain increased self-focus, a core feature in major depression. In addition the connections between the midline prefrontal cortex and limbic structures are thought to play role in the regulation of emotions. In a relatively recent study, Anand et al[34] reported decreased functional connections between ACC (anterior cingulate cortex) and other limbic structures in patients with depression. Decreased functional connectivity was estimated in neuroimaging studies by the temporal correlations of low frequency BOLD fluctuations (f<0.08Hz) between brain areas. They also reported increased activation of the limbic structures to negative stimuli in depression, putatively due to the decreased prefrontal regulation. To further evaluate their hypothesis, in a follow up study[35]; they measured the effect of antidepressants in these functional connectivities. They found that 6 weeks of treatment reversed the decreased connections and this correlated well with the reduction in the hyperactivation of the limbic system. Putting this information together, it seems that depression is not purely the end result of a non- or malfunctioning brain area, but it is much more a malfunction of a set of interacting brain areas: the malfunction of a network[29].

5. Neuroimaging studies in ECT

Studies using EEG were the first to support the generally believed doctrine that the major site of action is different than the site of side effects. First Fink M et al [36] demonstrated that the increase of slow wave activity in interictal recordings were associated with better outcome. Sackeim et al [37]demonstrated that topographic EEG changes associated with the adverse cognitive effects of ECT differed from those earlier found to be linked to clinical response, providing the hope for potential techniques which could increase the effect/side-effect ratio.

Structural neuroimaging could not detect ECT related changes in the brain (37), however there are several other studies indicating that individual differences can predict outcome. Given the facts that the hippocampus has a low seizure threshold and most of the adverse effects of ECT are related to memory, it was reasonable that Lekwauwa et al. focused primarily on this structure. They[38] reported that smaller hippocampal volume resulted in poorer ECT-related memory outcomes. Figiel et al[39] found that structural abnormalities in the basal ganglia and subcortical white matter were associated with the development of delirium during the course of ECT. Other studies indicate that neurogenesis in hippocampus might correlate with ECT efficacy. [40; 41]

The effect of ECT was also intensively studied with PET glucose and rCBF studies. Half of the studies found that ECT decreased activations in subgenual ACC, while the other half demonstrated the opposite effect. As McComrick et al[42] points out, the major difference between these sets of studies is the timing of the post-ECT scan. If imaging is acquired only a couple of days after the end of ECT treatment, the studies usually report a decrease in activation[35;43],while if the acquisition takes place after a couple of weeks the findings usually demonstrate an increase in activation[44-46]McCormick argues that this can be easily explained if we take into consideration what we know about epilepsy: postictally there is usually a decreased activation. Imaging too soon after the last ECT treatment could thus result in a decrease, whereas the therapeutic effect

can only be measured a couple of weeks later as the activation increases. Also, note that increases were mainly demonstrated with rCBF measurements[44-46], while decreases were measured with glucose metabolism.[47] At first glance this seems to be somewhat counterintuitive, but discrepancies in metabolism and blood flow actually might reflect something very profound about the biochemical reactions in a brain area. The ideal combination would be to measure the oxygen consumption and the glucose metabolism, as it was recently shown that this might have important implications.[48]

ECT is a form of psychosurgery?

As previously mentioned, functional neuroimaging studies in depression consistently show alterations in the subgenual ACC.[31; 32] .The subgenual ACC is now being targeted with deep brain stimulation (DBS) and this has shown to be an effective treatment. Originally it was thought that the basis of this type of treatment is that it causes a reversible lesion at a specific region. However, it has also been shown that there are other areas in the brain that can be effectively inhibited for the treatment of depression. Interestingly, these areas are all connected to the fronto-striatial network, and at this point it is thought that the stimulation not only affects one node in the brain, but through that node it influences the work of a complete neuronal network (fronto-striatal network). Can it be that the effect of ECT is also mainly dependent on its ability to alter neuronal networks in the brain?

The main theoretical question behind this study is whether ECT exerts its effect primarily by altering networks? Can we think about ECT as a crude way of doing DBS? With the help of advanced network paradigms and with the use of resting state fMRI techniques, can we potentially develop ECT that will be the outpatient equivalent of a DBS procedure?

## Research Design and Methods

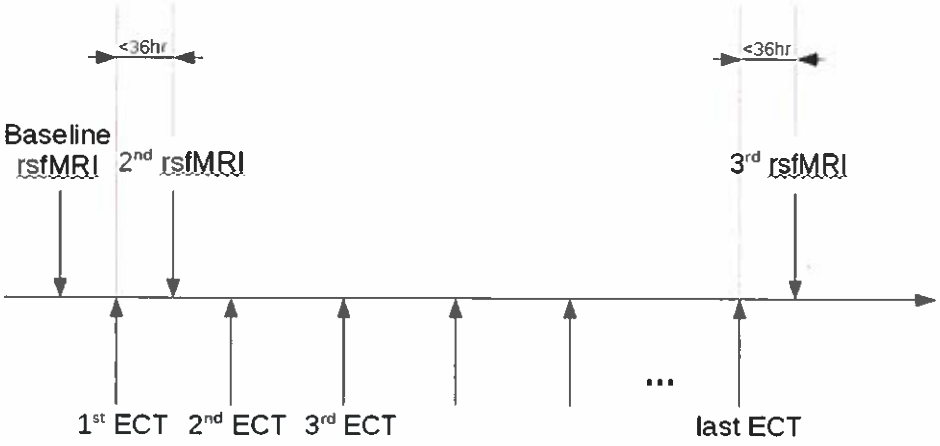
### 1. Study Overview

This is a prospective, random assignment, double blind, parallel group pilot study comparing the efficacy of bifrontal ECT performed with ketamine anesthesia to that performed with methohexital anesthesia in patients with a major depressive episode. We intend over a 2 year period, to recruit 24 patients who are scheduled to receive an acute course of ECT. Patients who are able and willing to provide written informed consent will be randomly assigned on a 1:1 ratio to receive either a course of bifrontal ECT using ketamine or methohexital anesthesia. Subjects will receive a standard acute course of ECT (3X/week) and depressive symptomatology will be monitored with the Hamilton Rating Scale for Depression (HRSD-24) before each treatment.

The primary outcome will be the number of treatments needed to achieve remission. Remission is defined as two consecutive HRSD scores $\leq 10$, and HRSD total score does not change $> 3$

points or remains < 6 at the last two consecutive treatments. For the secondary aim of this pilot study we will monitor cognitive changes before and after each ECT treatment, and at the end of the treatment course. In addition, we will collect data on other treatment parameters such as seizure duration, electroencephalogram (EEG) morphology, hemodynamic changes, and emergence of any psychotic symptoms post treatment.

Parallel with these procedures we will also collect magnetic resonance imaging (MRI) data on these subjects. The timeline of neuroimaging and it relation to ECT is illustrated in Figure 1.




MRI acquisition will consist of the following: On the day of imaging, the patient will be transported to the North Shore University Hospital 3T GE MRI suite. The patient will undergo an approximately 75 minutes long acquisition session. All subjects will receive structural (e.g., SPGR, FSE, FLAIR, DTI, and spectroscopy) and/or functional MRI exams. During the anatomical, DTI and spectroscopy images, the participating subject will be asked not to move, during resting stated fMRI, the subject will be asked to close her/his eyes and not to think anything particular, but to stay awake. During block or event related sessions, the patient will be shown different emotionally loaded images. These images will alternate and the patient will be asked to passively watch these pictures during the five minute acquisition period. These pictures will be chosen from the International Affective Picture System[49], and will be faces expressing different emotions. The International Affective Picture System assigns each image a valance and

an arousal value (derived from testing hundreds of healthy individuals over the span of 13 years). This makes it possible to chose only images with low arousal values (not only to avoid disturbing images but also to filter for nonspecific brain activations), and also to balance out the arousal levels between different emotional domains.

In addition to the imaging procedures detailed above, we also plan to acquire imaging data on healthy individuals with similar timeline. Healthy volunteers will be scanned three times; the first and second scans will be 24-48 hours apart, while the second and third scans will be two weeks apart. The imaging sessions will follow the same protocol as in the patients. The collection of control data is necessary in order to demonstrate that imaging findings are not due to acclimatization to scanner environment or other confounding sources.

## 2. Subject Recruitment

Twenty four male and female patients with Unipolar or Bipolar Depression who are referred for an acute course of ECT will be recruited for the study. Recruitment will occur at North Shore LIJ-Zucker Hillside Hospital.

The Zucker Hillside Hospital (ZHH) is the major psychiatric facility associated with the health system. Subjects will be recruited from the inpatient and outpatient units. The ECT unit in ZHH is an active unit providing ECT treatments on approximately of 14 patients daily. Prospective subjects will be approached for study enrollment by the ECT psychiatrists who participate in this study and/or a research fellow in ECT. Upon subject's agreement, a meeting with the research staff will be scheduled to begin the informed consent process. The study purpose, procedures, risks, benefits and alternatives will be discussed. After informed consent is signed, eligibility will be confirmed by diagnostic and psychometric assessments by trained raters as described in the screening visit. Based on our previous experience in enrolling patients in other trials, we anticipate that we can accomplish the recruitment goal of 24 patients over two years in the proposed study.

We also plan to recruit 10 healthy subjects for the imaging part of the study, through newspaper advertisement and word of mouth. The wording of the advertisement is attached to this protocol.

## 3. Inclusion/ Exclusion Criteria

Inclusion Criteria for patients:

1. Male or female subjects 18 to 70 years of age

2. DSM IV diagnosis of Major Depression (296.3), unipolar without psychotic features or Bipolar I or Bipolar II Depression without psychotic features confirmed by SCID-IV interview
3. Pretreatment 24-item Hamilton Rating Scale for Depression score $\geq 21$
4. Subjects must have an initial score of at least 20 on the MADRS at screen
5. ECT is clinically indicated
6. Patient is competent to provide informed consent

Exclusion Criteria for patients:

1. Lifetime DSM-IV diagnosis of schizophrenia, schizoaffective disorder, psychotic depression or any other psychotic disorder as defined in the DSM-IV
2. Current (within the last year) diagnosis of anxiety disorder, obsessive- compulsive disorder, or eating disorder that precedes the onset of the current episode of depression
3. Current diagnosis of delirium, dementia, or amnestic amnesiac disorder
4. Diagnosis of Mental Retardation
5. Baseline Mini Mental State Exam (MMSE) score < 21 or a total score falling two standard deviations below the age- and education-adjusted mean, whichever is less
6. Any active general medical condition or CNS disease which can affect cognition or response to treatment
7. Current (within the past three months) diagnosis of active substance dependence, or active substance abuse within the past week
8. Lifetime history of ketamine or phencyclidine (PCP) abuse or dependence
9. ECT within three months
10. The presence of any known or suspected contraindication to methohexital or ketamine including but not limited to known allergic reactions to these agents, uncontrolled hypertension, arrhythmia, severe coronary artery disease and porphyria
11. Pregnancy
12. Status 4 or greater according to the criteria of the American Society of Anesthesiologists
13. MRI contraindications

Inclusion Criteria for healthy volunteers:

1. Male or female older than age 18
2. Patient is competent to provide informed consent

Exclusion Criteria for healthy volunteers:

1. Lifetime history of major chronic mental illness, such as schizophrenia or bipolar disorder
2. Lifetime history of psychiatric hospitalization because of any mental illness
3. Mental illness that needed psychological or pharmacological treatment in the past 3 years
4. Any neurodevelopmental or neurodegenerative disease, or stroke or positive findings on past head CT or brain MRI

5. Pregnancy
6. Lifetime history of ketamine or phencyclidine (PCP) abuse or dependence
7. Current (within the past three months) diagnosis of active substance dependence, or active substance abuse within the past week
8. Hamilton Rating Scale for Depression (HRSD-17) is more than 7
9. MRI contraindications

The majority of these criteria reflect usual clinical characteristics of patients receiving ECT. We include patients with Unipolar and Bipolar depression without psychotic features since recent literature indicate that ECT has equivalent efficacy in Biporal and Unipolar depressive patients. Moreover, Diazgranados et al in a recent study suggest that a single intravenous infusion of ketamine produced rapid antidepressant effect in bipolar depressive patients. Ketamine was well tolerated and the reported adverse events were similar to those reported in unipolar depressive patients received ketamine. We exclude patients with schizoaffective disorder and schizophrenia because they often require lengthier treatment courses and present with psychotic and cognitive deficits, specific to their illnesses, which may confound our results. We also exclude other diagnostic groups such as patients with neurologic illnesses, dementia, delirium, mental retardation, and active substance abuse/dependence because of possible confounding effects on cognition. Patients who have received ECT within the preceding three months will be excluded for the same reason. Patients who have a lifetime history of ketamine or PCP abuse or dependence will be excluded to protect them from exposure to their drug of abuse or dependence, or in the case of PCP, to a drug similar in mechanism of action. Patients with a current (i.e. within the last year) diagnosis of an anxiety or eating disorder which preceded the current episode of depression will be excluded because their anxiety or eating disorder symptoms may overlap with those of depression and confound psychopathology ratings. Additionally, such patients may have a differential clinical response to ECT. Since we are exploring hemodynamic changes we will exclude pregnant women to avoid confounding the results with the hyper dynamic state of pregnancy.

If during screening the patient is found to be ineligible for the ketamine part of the study (e.g. Hamilton score is low) but patient would undergo ECT for clinical indications, we will still offer the patient to participate in the imaging part of the study, since the patient can still significantly contribute to the secondary aim of this study. In this case (when patient participates only in the imaging part) the inclusion criteria will be only 5, and 6, and the exclusion criteria will be 9, 11 and 13 respectively.

### 4. Randomization

**Method:** The permuted block method of randomization will be used to assign patients to one of the treatment conditions. Block size will be varied to minimize the likelihood that the blind will be broken by raters who are blind to assessment. For safety purposes the anesthesiologist and

the ECT psychiatrist will not be masked to the anesthetic agent used. Randomization will be performed by the research coordinator and will be communicated to the ECT psychiatrist and the anesthesiologist.

### 5. Medication Washout

As it is common in clinical practice, every effort will be made to discontinue psychotropic medications before the onset of ECT. In any case no psychotropic medications will be allowed 5 days after the first treatment. The only psychotropic medication allowed during the study is lorazepam up to 3 mg/day for anxiety or insomnia.

### 6. ECT Procedures

ECT will be administered following the standard 3 times per week schedule (Monday, Wednesday, Friday) until remission is achieved (defined by an HRSD-24 score of 10 or less) or until a patient is declared a non remitter (see criteria, page 15). Subjects will be withdrawn from the study if side effects become limiting, or if either the patient or principal investigator determine that ECT should be discontinued. All patients will be treated with moderately suprathreshold stimulus doses. Threshold will be determined at the first treatment and doses will be increased at subsequent treatments as needed to insure adequacy of seizures. (see section d) The average total number of ECT per patient is expected to be approximately 8 and will not exceed 15 in any case.

Both inpatients and outpatients will he brought to the ECT treatment area in the morning on the day of treatment and an intravenous catheter will be introduced and remain in place until the treatment has been completed. Blood pressure, pulse rate, ECG, and pulse oximetry will be monitored prior to anesthetic induction and continuously during the procedure.

#### a. Electrode placement.

Standard bifrontal electrode placement will he used in all subjects.

#### b. Anesthetic procedures.

Anesthetic procedures will be followed according to the American society of Anesthesia Standard Guidelines. Participants will be instructed to fast for 8 hours prior to ECT session. Approximately two minutes prior to the administration of the anesthetic glycopyrrolate 0.2 mg IV will he administered. Then the anesthetic (either methohexital 0.5-1 mg/kg or ketamine 1-2 mg/kg) will be administered by rapid bolus injection. After determining loss of consciousness succinylcholine 0.5-1.5 mg/kg IV will be administered. This doses may be adjusted up or down at subsequent treatment sessions depending on the patient's response. Prior to the injection of the succinylcholine a blood pressure cuff will be inflated on the right ankle to 250 mm of mercury to serve as a tourniquet and prevent the flow of succinylcholine to the right foot. This will enable the motor manifestations of the seizure to be observed and recorded. From the onset

of anesthetic response and until the return of spontaneous respiration, patients will he oxygenated with 100% oxygen positive pressure using a Mapelson D circuit. Particular attention will be paid to ensuring hyper-oxygenation prior to seizure induction. Oxygenation will be briefly interrupted during the passage of the electrical stimulus. Pulse oximetry will be used to monitor oxygenation. After ECT administration, participants will be monitored by nursing staff and will not leave the ECT treatment room until they have attained fully recovery.

### c. EEG recording.

A one channel (4-lead) automated EEG recording will he made during each ECT session using left and right fronto-mastoid electrode placements. Pre- lubricated, disposable EEG electrodes will be used (Somatics. Inc., Lake Bluff, IL). The adequacy of the EEG recording will be ascertained prior to the administration of the treatment. In the event of a low-amplitude at baseline, the sensitivity of the EEG amplifier will be increased. The digital recorder strip for the complete treatment session will be retained and identified with the patient's identification number, the date, and the treatment number.

### d. First treatment titration procedure.

Seizure thresholds are determined at the first treatment. This method, introduced by Sackeim et al[27] allows delivery of a series (usually1-3) of successively higher stimulations until a seizure is elicited. Two threshold determination schedules are used. One for patients < 50 years of age since younger patients have a lower seizure threshold and the other for patients >50 years of age or older.[50;51] Dosing at subsequent treatments is set 50 % above seizure threshold, thereby ensuring seizure adequacy without excessive cognitive effects.
Subconvulsive stimuli (i.e. "missed" seizures) and short seizures during the course are followed by stimuli at 50 % greater charge after a waiting period of at least 20 seconds.

**Table 1 Titration Procedure**

| Electrode Placement/Age | Threshold % Energy | Dose at Subsequent ECT Treatment % Energy (Bilateral) |
|---|---|---|
| Bifrontal - Under 50 | 5 | 10 |

| | | |
|---|---|---|
| | 10 | 15 |
| | 20 | 30 |
| | 40 | 60 |
| | 80 | 100 |
| Bifrontal - 50 years and older | 10 | 15 |
| | 20 | 30 |
| | 40 | 60 |
| | 80 | 100 |
| | 100 | 100 |

## 7. Assessment Instruments and Procedures

### a. Raters

All assessments will be performed by trained raters. Raters will be masked to the anesthetic agent used in ECT procedure. For safety purposes the anesthesiologist and the treating psychiatrist will not be masked to the anesthetic agent used. Raters will not be physically present in the treatment room during the procedure.

### b. Assessment Instruments

The primary outcome measure is the HRSD-24 which will be administered at baseline and before each treatment.[52] The HRSD-24 is a semistructured interview designed to rate the severity of depressive symptoms in patients with a primary depressive illness. We will use the 24- item version, which includes three items in addition to the original 21 (i.e., Helplessness, hopelessness, worthlessness).
Brief Psychiatric Rating Scale (BPRS) (Hillside Anchored version)[53;54] BPRS will be administered at screening and after last ECT treatment.

Psychotic symptoms will be measured by the four item positive symptoms subscale (consisting of suspiciousness, hallucinations, unusual thought content, and conceptual disorganization) of the Brief Psychiatric Rating Scale (BPRS). After each ECT treatment BPRS+ will be administered as following: after full orientation recovery, two hours post ECT. If any of the items are positive (2 or higher) BPRS+ will be re administered at 4 hours post ECT. If symptoms persist, patients will be further evaluated by a study psychiatrist and will be treated clinically as needed. Of note, that as part of standard care, patients are under constant observation and monitoring after ECT until they are deemed stable to be discharged from the unit.

Clinician-Abministered Rating Scale for Mania (CARS-M): The CARS-m is a brief, clinician-administered, semistructured interview, which rates presence versus absence of a symptom, its severity, and symptom change in response to treatment. It is used to characterize manic behavior, but also to capture psychotic symptoms. These items yield two subscale scores one for mania (items 1-100 and one for psychosis (items 11-15).[55]

The secondary outcome measures are the scores of neuropsychological (NP) battery. The neuropsychological (NP) battery is administered to all subjects at baseline (prior to the first ECT), on ECT #4 and following the end of the acute phase of ECT. In addition the MMSE will be performed prior to each ECT session and assessment of postictal recovery of orientation after each ECT session.

The neuropsychological test battery consists of the following instruments:

- Reading subtest of the Wide Range Achievement Test, 3rd Edition (WRAT-3), which will only be administered at baseline
- Mini- Mental State Examination (MMSE)
- Postictal Recovery of Orientation
- Rey Auditory Verbal Learning Test (RAVLT)-Immediate
- Autobiographical Memory Interview – Short Form (AMI – SF)
- Subjective Memory Questionnaire (SMQ)
- The Stroop Color Word Test (SCWT) (Golden version)
- Trail Making Test Part A & B
- WAIS-III Digit Symbol
- Wechsler Adult Intelligence Test-Third Edition (WAIS-III), Digit Span Subtest
- Controlled Oral Word Association Test (COWAT)
- N-Back

The cognitive domains to be assessed include orientation/global functioning, verbal anterograde memory, autobiographical (retrograde) memory, and subjective memory.

***Global Functioning***: The Reading subtest of the Wide Range Achievement Test, Third Edition (WRAT-3) will be administered at baseline to provide an estimate of premorbid intellectual functioning. The reading score in particular has shown a moderate correlation with WAIS Full Scale IQ scores and provides a sufficient estimate of average IQ levels. This has also been found to be true among individuals exhibiting cognitive decline.[56] The Mini-Mental State Exam (MMSE)[57] is a measure of global cognitive functioning with a maximum score of 30. Reliability and validity have been well established[58] and alternate forms are available.

***Orientation*** Postictal recovery of orientation will be assessed following every ECT treatment utilizing the Sobin method.[59] According to this method, once the patient gains spontaneous respiration, orientation will be continually assessed (in 15-minute intervals) by asking the patient

to state his/her name, age, date of birth, day of the week, and current location. The assessment will continue until the patient correctly answers all five questions or until a time limit of 90 minutes is reached.

***Memory***: One of the most sensitive formats of assessing anterograde verbal memory is word list learning, given its relative freedom of associative context.[60] The Rey Auditory Verbal Learning Test (RAVLT) is brief and easy to administer and has been well-validated. Equivalent alternate forms are available.[61]

Retrograde amnesia for autobiographical information will be assessed by the Autobiographical Memory Interview (AMI), which was originally developed by Weiner, Squire, and colleagues[62], and later expanded by Sackheim et al. [63]

The Subjective Memory Questionnaire (SMQ) will be used as a self-report measure of memory functioning. Most questions on this measure require an evaluation of memory or learning for specific material and cover a suitable range of everyday memory activities.[64]

Wechsler Adult Intelligence Test-Third Edition (WAIS-III), Digit Span Subtest - The WAIS-III Digit Span subtest assesses immediate span of auditory attention as well as working memory. In this task subjects are required to repeat sequences of verbally presented digits forward and backward[65].

WAIS-III, Digit Symbol Subtest - The WAIS-III Digit Symbol subtest task measures both visual scanning and graphomotor speed. This subtest requires subjects to match meaningless symbols with the numbers 0-9 based on a key presented at the top of the form.[65]

Trail Making Test Part A & B - The Trail Making Test (Parts A & B) is a measure of attentional resources. Part A is a simple scanning task in which the subject is required to connect randomly arrayed numbers in order, while the more demanding Part B requires subjects to sequentially alternate between numbers and letters. Score on the test is the time required to complete each sequence. Part B is primarily conceptualized as a measure of the frontal lobe "executive" functions of visual search, set-switching and conceptual flexibility.[65]

The Stroop Color Word Test (SCWT) (Golden version) The SCWT is a commonly used task measuring selective attention and inhibitory control, or cognitive control. This test is designed to measure the ease with which a person can shift his/her perceptual set to conform to changing demands and suppress habitual response in favor of a more effortful one .[65]

Controlled Oral Word Association Test (COWAT) (Benton & Hamsher, 1989): This is a measure of sustained verbal fluency.[66] It requires the subject to produce as many words as possible that begin with specific letters in a 60-second period. Two matched sets of letters (CFL and PRW) are used as alternate forms of the test. The score is the sum of all correct words produced during the three 60-second trials with adjustments for age, sex, and years of education.

The *n*-back task requires on-line monitoring, updating, and manipulation of remembered information and is therefore assumed to place great demands on a number of key processes within working memory. It is a computerized continuous performance task. The subject is presented with a sequence of stimuli, and the task consists of indicating when the current stimulus matches the one from *n* steps earlier in the sequence. The load factor *n* can be adjusted to make the task more or less difficult.

Treatment side effects will be measured using the Treatment Emergent Side Effects Scale (TESS)[67] This 49-item scale assesses the presence and severity of a range of potential side effects including 1) behavioral toxicity such as agitation; 2) neurological effects such as tremor; 3) cardiovascular effects such as palpitations; 4) autonomic effects such as dry mouth; and 5) other effects.

### c. Timing of Assessments

**Table 2: Timing of Assessments**

| Assessment | Baseline[1] | 3X weekly before ECT | 3X Weekly following ECT | ECT # 4 | After last ECT[2] |
|---|---|---|---|---|---|
| **Informed Consent** | X | | | | |
| **Past Psychiatric History** | X | | | | |
| **Medical Evaluation** | X | | | | |
| **HRSD-24** | X | X | | | X[3] |
| **BPRS** | X | | | | X |
| **BPRS positive items** | | X | X[5] | | |
| **SCID** | X | | | | |
| **Neuropsychological Battery** | X | | | X[2] | X[4] |
| **Reorientation time** | | | X | | X |
| **MMSE** | | X | | | |
| **TESS** | X | | | | X |

[1] Performed within 24 hours before the first ECT; [2] 24hrs post ECT; [3] 24-72 hrs post last ECT; [4] 1 week post last ECT [5] BPRS+ after full recovery, at 2h, at 4h if $BPRS+_{2h} > 2$

### d. Outcome Criteria

1. **Remitter criteria**

   (a) ≥ 60% decrease from baseline in HRSD total score, *and*

   (b) HRSD ≤ 10 on two consecutive ratings, *and*

   (c) HRSD does not change > 3 points on last 2 consecutive treatments. We do not define a specific minimum or maximum number of ECT for a patient to be classified as a remitter.

2. **Non-remitter criteria**

   (a) patient does not reach above remission criteria, *and*

   (b) has at least 10 treatments, *and*

   (c) reaches a plateau defined as no clinical improvement (< 3 point decrease in HRSD after last 2 consecutive treatments).

*Drop-outs* are patients who discontinue treatment before they can be declared remitters or *non-remitters*. Premature exits in this study will be analyzed as non remitters. Criteria for *premature exits* are as follows:

3. **Premature exits**

   (a) consent for ECT or study participation is withdrawn *before 10 ECT have been administered, or*

   (b) initial ST is 80% or higher, *or*

   (c) ECT is discontinued for clinical or other reasons *before 10 ECT have been administered*, or

   (d) more than one week separates two treatments.

## 8. Risks

There are no additional significant risks due to the study procedures. The safety of ECT is well established. The risks of the procedure are described at the standard institutional consent form that the patients sign before treatment. Patients will be approached to sign informed consent for the study only after they have consented to ECT.

Possible but infrequent complications of ECT may include headaches, myalgia, and fractures (from the muscular contractions followed by seizures), chipped or lost teeth, spontaneous seizures and, in extremely rare conditions, death.

Methohexital is the anesthetic most commonly used in for ECT. Possible adverse events of methohexital anesthesia include hypotension, pain at the injection site nausea, emesis, muscle hyperactivity (twitching, shivering, tremors, involuntary muscle movements or convulsive like movements) excitation, headache, lethargy, restlessness, and delirium upon wakening.

Ketamine is widely used in pediatric populations and it has proven to be safe. The incidence of psychotic-like symptoms in adults although more common than in pediatric population, are usually transient, rarely lasting longer than two hours. Moreover, the psychomimetic effects of ketamine are rarely observed with ECT and even then, are successfully managed with the use of a benzodiazepine. Other possible adverse events in both anesthetic and sub-anesthetic doses include transient increases in blood pressure and pulse rates as well as ataxia, nausea, dizziness, headache and confusion.

As for every medication there is the rare possibility of an allergic reaction.

All subjects will sign informed consent for the standard ECT treatment and for the anesthetic procedure and they will sign informed consent for participating in the study.

**MRI**

There are no special benefits anticipated from participation in these studies. The risks of f-MRI scanning are minimal. There is no ionizing radiation involved in MRI, and there have been no documented significant side effects of the magnetic fields and radio waves used on the human body to date. However, because the effects of strong magnetic fields on a fetus are not well documented at this time, pregnant women will be excluded from the study. People have been harmed in MRI machines when they did not remove metal objects from their clothes or when others left metal objects in the room. All necessary precautions will be taken to prevent inadvertent presence of metal objects in the MRI room. Some subjects, even those without known history of claustrophobia may experience discomfort or even panic attacks in the enclosed setting of the magnet. All efforts will be taken to first calm subjects down and next to decide together with the participant whether or not to continue study participation.

## 9. Adverse Event Reporting

Side-effects will be monitored by the study physician and self reports. Treatment side effects will be measured using the Treatment Emergent Side Effects Scale (TESS). Reported adverse events will be evaluated and treated according to standard treatments procedures. In the case of a serious or intolerable adverse event subjects will be withdrawn from the study and he will be referred for treatment if necessary. Serious adverse events will be reported to IRB in no more that 24 hours after occurrence or after the ECT psychiatrist is informed.

## 10. Data Security

Subject information will be stored electronically and controlled by the Principal Investigator. Identifiers will be separated from medical information and other data and will be replaced with a linkage code. Access to Protected Health Information (PHI) contained within the data base will be restricted to ZHH investigators.

Information linking the linkage codes to the subjects' PHI will be stored in a secure location in a locked file cabinet in the locked study coordinator's office separate from the medical information. Access to the information linking the linkage codes with each subject's respective PHI will be granted only to study personnel on a need to know basis as approved by the principal investigator of this study.

Data will be stored in the database for an indefinite period of time.

Data will be analyzed by the Zucker Hillside Hospital Department of Psychiatry Research Biostatistics Unit.

## 11. Benefits

Subjects receiving ketamine anesthesia may require fewer ECT sessions to achieve remission and may have less cognitive side effects as compared to commonly used methohexital anesthesia.
The results of this pilot study will guide us to design a larger and more definitive study and apply for NIMH funding.

## 12. Financial Disclosures

The ECT procedures will be billed to the insurance carriers of the research subjects. There will be no reimbursement for participating in the study.

## 13. Data Analysis

To test whether the time to remission is different between the ketamine and the methohexital groups, a survival analysis will be performed. The outcome event will be remission, and Kaplan-Meier curves will show the percent of patients not in remission as a function of time on study. A log-rank test will be used to test for differences between the time to remission in the two groups. Patients who drop out of the study prior to achieving remission or who continue to the end of the study period without achieving remission will be analyzed as censored at the time of last observation.

For Aim 1, to test whether the rate of change in the HRSD score over time is different in the two treatment groups, a mixed model for longitudinal data will be used. The fixed effects are

treatment group and time on study, and the random effect is subject. The data will be examined to see whether a linear function of time is appropriate. If not, either the data will be transformed to achieve linearity, or another form (e.g., quadratic) of model will be considered. This model will yield estimates for slopes (rates of change in HRSD scores per visit) for each treatment group, and the groups will be compared by testing whether the slopes are significantly different from one another.

For Aim 2, to test whether the rate of change in the various measures of cognitive function over time is different in the two treatment groups, a mixed model for longitudinal data will be used for each of the measures. As above, the fixed effects are treatment group and time on study, and the random effect is subject. The data will be examined to see whether a linear function of time is appropriate. If not, either the data will be transformed to achieve linearity, or another form (e.g., quadratic) of model will be considered. As above, the model will provide estimates of the slopes measuring the rates of change in scores per visit for the two treatment groups; and the treatments will be compared by testing for a difference between the slopes corresponding to the two groups.

Since this is a pilot study, the goal is to estimate the magnitude of the effect sizes for use in designing a subsequent study. With 12 patients randomized to each of the two treatment groups, there is only 45% power with an alpha level of 5% to detect a difference of 50% remission rate in the methohexital group and an 80% remission rate in the ketamine group at visit 8. For the other aims, which look at the change in scores on various rating scales over time, there will be 80% power with an alpha level of 5% (2-sided) to detect a difference between the slopes (measuring rate of change in scores on tests per visit) for the two treatment groups of magnitude $0.05\sigma$, where $\sigma$ is the standard deviation of scores in either treatment group at a single visit. If, for example, the standard deviation of the HRSD scores is 5.0, then there will be power to detect an increased rate of improvement in the ketamine group of 0.25 points per visit, corresponding to an average improvement of 2.0 more points per 8 visits in the ketamine group than whatever improvement is observed in the methohexital group (Diggle et al 1995).

Given the recognition that, with the small sample size, power will be low, the primary focus of analysis is to determine whether ECT with ketamine anesthesia compared to ECT with methohexital anesthesia produces a clinically significant effect, i.e., one that, even if it does not reach statistical significance, would justify a larger clinical trial to replicate effect size. We expect a mean number of 8 treatments to remission based on the results of a Consortium for Research in ECT paper.[2]

Our specific hypothesis is that ECT will decrease functional connectivity in the Default Mode Network (time-wise hypothesis). We also think that the decrease in the expression of this network will correlate with the effectiveness of the ECT, or at least will show a difference

between responders and non-responders (group-wise hypothesis). In order to detect network changes, we will calculate seed based correlation, ICA network expressions and amplitude measures of the networks.

For Aim 2 B, Block and event related functional MRI designs will be analyzed with the standard General Linear Model implemented in both SPM (http://www.fil.ion.ucl.ac.uk/spm/) and FSL (www.fmrib.ox.ac.uk). For functional connectivity we will use seed-based correlation analysis, based on previously identified seed regions[12], and model-free ICA, using temporal concatenation to generate group-level components and dual regression to generate individual participant maps. For amplitude measures at each voxel we will use FFT-based ALFF and its normalized variant fALFF.

## Preprocessing, Overview.

All available resting-state scans were preprocessed using both AFNI (http://afni.nimh.nih.gov/afni) and FSL (www.fmrib.ox.ac.uk). Specific commands can be found in the preprocessing scripts that are released at www.nitrc.org/projects/fcon_1000. The first four time points of every scan will be discarded, to remove possible T1 stabilization effects, the data will be corrected for motion by aligning each volume to the mean image volume using Fourier interpolation in AFNI. Then the data will be spatially smoothed using a 6-mm FWHM Gaussian kernel. Mean-based intensity normalization will be done by scaling all volumes by the same factor (10,000).

*Seed-based correlation analyses.* The data will be temporally filtered using both a high-pass (Gaussian-weighted least squares straight-line fitting, with $f$ = 100.0 s) and low-pass (Gaussian low-pass temporal filtering, with a HWHM of 2.8 s) filter, followed by linear detrending to remove any residual drift.

*Independent component analysis-Temporal concatenation group analysis.* Consistent with common practice, temporal filtering for ICA analyses will be limited to high-pass filtering (Gaussian-weighted least squares straight-line fitting, with $f$ = 100.0 s).

*Dual regression.* This step will use the same preprocessed data as will be used in the seed-based correlation analyses.

*ALFF/fALFF.* No temporal filtering will be carried out, because the data will be examined in the frequency domain within select bands[68], (fALFF). Temporal despiking with a hyperbolic tangent squashing function will be performed, however, to limit extreme values. Linear trends will then be removed from the data.

*Registration and normalization.* The skull will be removed using AFNI, registration of each individual's high-resolution anatomic image to a common stereotactic space [the Montreal Neurological Institute 152-brain template (MNI152); 3 mm isotropic voxel size] will be done using a 12 degrees of freedom linear affine trans-formation (FLIRT). The resulting transformation will then be applied to each individual's functional dataset.

## Seed based correlations

**Nuisance signal regression.** Consistent with common practice in the rs-fMRI literature, nuisance signals will be removed from the data via multiple regressions before functional connectivity analyses will be performed. This step is designed to control for the effects of physiological processes, such as fluctuations related to motion and cardiac and respiratory cycles. Specifically, each individual's 4D time series data will be regressed on nine predictors: white matter (WM), cerebrospinal fluid (CSF), the global signal, and six motion parameters. The global signal regressor will be generated by averaging across the time series of all voxels in the brain. The WM and CSF covariates will be generated by segmenting each individual's high-resolution structural image (using FAST in FSL). The resulting segmented WM and CSF images will be threshold to ensure 80% tissue type probability. These threshold masks will then be

applied to each individual's time series, and a mean time series will be calculated by averaging across time series of all voxels within each mask. The six motion parameters will be calculated in the motion-correction step during preprocessing. Movement in each of the three cardinal directions (X, Y, and Z) and rotational movement around three axes (pitch, yaw, and roll) will be included for each individual. We are aware of the potential problem that the global signal removal might cause by introducing anti-correlating artifacts. Thus we will always compare these calculations to a similar protocol where global signal will not be removed. **Seed selection.** Six 7.5-mm-radius seed regions of interest (ROIs) (containing 33 voxels) centered on the coordinates previously used by Fox et al[12]. will be created to examine functional connectivity for each of six regions, three regions within the "task-positive" network and three within the "default mode" network. The ROIs within the task-positive network will be located in the IPS (-25, -57, 46), the middle temporal region (MT+; -45, -69, -2), and the right frontal eye field (FEF) region of the precentral sulcus (25, -13, 50). The default mode network seed ROIs will be located in the left lateral parietal cortex (LP; -45, -67, 36), medial prefrontal cortex (MPF; -1, 47, -4), and PCC (-5, -49, 40).

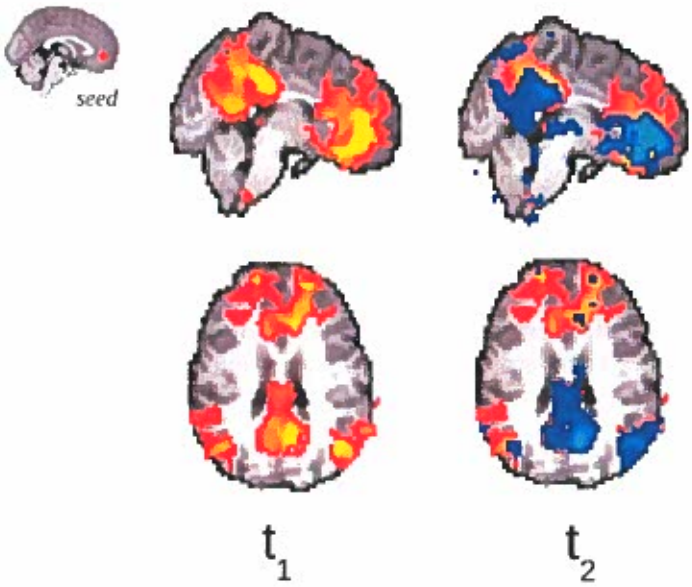



**Figure 2**

**Individual seed-based functional connectivity analysis.** First, each individual's residual 4D time series data will be spatially normalized by applying the previously computed transformation to the MNI152 standard space. Then the time series for each seed will be extracted from these data. Time series will be averaged across all voxels in each seed ROI. For each individual

dataset, the correlation between the time series of the seed ROI and that of each voxel in the brain will be determined. This analysis will be implemented using 3dfim+ (AFNI) to produce individual-level correlation maps of all voxels that will be positively or negatively correlated with the seed's time series (Figure 2). Finally, these individual-level correlation maps will be converted to Z-value maps using Fisher's r-to-z transformation.

### ICA-Dual regression

The dual-regression approach will be used to identify, within each subject's fMRI data set, subject-specific temporal dynamics and associated spatial maps. This involves (I) using the full set of group-ICA spatial maps in a linear model t (spatial regression) against the separate fMRI data sets, resulting in matrices describing temporal dynamics for each component and subject, and (ii) using these time-course matrices in a linear model t (temporal regression) against the associated fMRI data set to estimate subject-specific spatial maps. Finally, the different component maps are collected across subjects into single 4D images (1 per original ICA map, with the fourth dimension being subject identification) and tested voxel-wise for statistically significant differences between groups using nonparametric permutation testing (5,000 permutations). This results in spatial maps characterizing the between-subject/group differences (Figure 3).

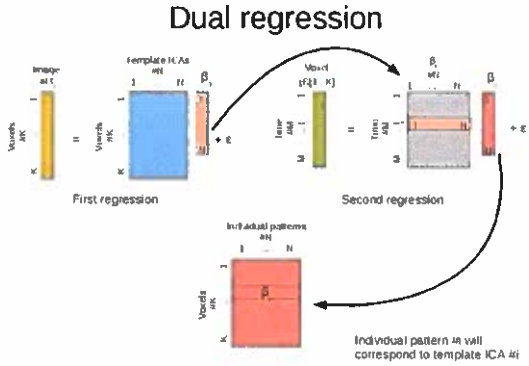



*Figure 3. Dual regression*

The biggest advantage of this technique is that it will create functionally and anatomically corresponding spatial maps for every individual, thus making the patterns comparable across subjects. In traditional approaches individual ICA resulted in components where no straightforward comparison was possible.

**Amplitude measures**

Amplitude of spontaneous low-frequency fluctuations. To examine the potentially meaningful information contained within the ALFF, two fast-Fourier transformation (FFT)-based indices, ALFF and fALFF, will be used to compute the amplitude of low-frequency fluctuations in the frequency domain. For each individual, ALFF and fALFF will be computed to identify those voxels with significantly detectable low-frequency fluctuation amplitudes. Specifically, at each voxel, ALFF is calculated as the sum of amplitudes within a specific low frequency range (0.01-0.1 Hz). fALFF is the normalized ALFF, calculated by dividing the ALFF value by the total sum of amplitudes across the entire frequency range measured in a given time series. Voxelwise ALFF and fALFF maps will be calculated for each participant in native space, and then will be transformed into the MNI152 standard brain space with 3-mm isotropic voxel size. Before statistical analyses, each individual ALFF or fALFF map will be Z-transformed (i.e., by subtracting the mean voxelwise ALFF or fALFF obtained for the individuals entire brain, and then dividing by the corresponding SD) to improve its suitability for group-level parametric analyses. The individual Z-transformed ALFF or fALFF maps will be used in subsequent group- and center-level analyses. Multiple comparisons will be corrected at the cluster level using Gaussian random field theory (min $Z>2.3$; cluster significance: $p<0.05$, corrected).

**Group analysis**

Our main goal in our analysis is to determine group-wise effects. The inter-subject variability however poses the main obstacle to gain meaningful effects. We will use our time-wise data to "subtract" measures between time points in the same individual, and analyze our data with repeated measure ANOVA (one factor is time point (intra-subject), other is group (inter-subject)).

Group comparison of the seed based correlation measures is straightforward, correlation values between the vmPFC and other DMN regions and subgenual cingulate will be used to detect any interaction between factors (time and group (responders and non-responders)).

The group analysis of ICA networks will be carried out by dual regression method, as it is presented on Figure 3. Individual network patterns will be obtained, and these individual patterns will be used in a second level analysis with SPM, where voxel based repeated measure ANOVA will be calculated. Similarly individual amplitude maps will be analyzed with SPM.

**Sample Size and Power**

The primary objective of this study is to examine and validate the differences in neuroimaging changes and network expressions across different time points during the ECT treatment. We will use repeated measure ANOVA to analyze each of the neuroimaging measures between different timepoints. Traditional power analysis in neuroimaging is challenging not only because of the inherent multiple comparisons in our studies, but also due to the fact that different voxels have different signal to noise ratio, thus effect sizes. One possible approach would be to estimate the

effect size[69]. In order to do that, we have to estimate the distribution of the magnitude of signal change and the within subject and between subject variance. In a motor area the signal change can be well above 1%, but with cognitive or perception tests the signal is usually around 0.5-1%[69] . According power analysis calculations with these parameter estimates it was shown that 80% power can be reached with $N$=20 sample size. [69]Indeed, targeting for 20 subjects in neuroimaging studies is a common practice.

**Future Studies:** MRI images and diagnostic information will be kept in an IRB-approved data repository (IRB # 06.04.089; P.I.: Phil Szeszko). All study information will be kept private and identifiable information will only be released with participant permission. Participants in the current study may also be contacted about the possibility of participating in future studies.

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