Spinal Cord Stimulation for the Treatment of Major Depressive Disorder

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Spinal Cord Stimulation as Treatment for Major Depressive Disorder

Project Summary (Abstract):

Major depressive disorder (MDD) is a recurrent and chronic mood disorder that affects 14% of the adult population during their lifetime. Current treatment options are partially effective and the neurobiology of MDD is largely unknown. Recent evidence points to an important role of brain-body communication in the integration of mood and therefore in depression. Information travelling from the body to the brain through the dorsal horns in the spinal cord is essential to provide consciousness of emotional experience in a process called interoceptive awareness. This information is then used by the brain to adjust bodily function through hypothalamic and autonomic outputs. Increased sympathetic activity and somatic symptoms have been documented in MDD and suggest disturbed brain-body communication. Spinal cord stimulation (SCS) has been used in the past to decrease sympathetic activity and modulate spinal input to the brain. Indirect evidence suggests that SCS might have antidepressant effects. Transcutaneous spinal direct current stimulation(tsDCS) devices represent an effective, non-invasive, low cost alternative to surgically implanted SCS devices. We believe that extant data support our overarching HYPOTHESIS that an altered sensory input to the brain through the dorsal horns of the spinal cord contributes to the pathophysiology of depressive symptoms and that tsDCS will be effective and safe in treating MDD by decreasing sympathetic activity and restoring metabolic function. Thus, we aim to 1) determine the efficacy and safety of tsDCS in adult patients with MDD and 2) investigate interoceptive awareness, somatic symptoms, autonomic and metabolic regulation as potential mediators of antidepressant response to tsDCS. We predict that 1) Active tsDCS treatment will result in a greater decrease in depressive symptom severity compared to Sham tsDCS in adult patients with MDD, 2) active tsDCS will be safe and well tolerated in adult patients with MDD and 3) change in interoceptive awareness, somatic symptoms, and autonomic and metabolic parameters will be associated with change in depressive symptom severity. To accomplish these aims, we will conduct an 8-week, double blinded, randomized, sham controlled, parallel group, pilot clinical trial study design. A total of 20 adult antidepressant-free MDD patients will be randomized to receive Active (n=10) or Sham (n=10) tsDCS protocols for 8 weeks in a 1:1 ratio. As an initial test of our hypothesis, we will combine the use of a tsDCS device, psychometric instruments to diagnose MDD (M.I.N.I.), and measures of depressive symptom severity (MADRS and PHQ-9), somatic symptoms (4DSQ), interoceptive awareness (MAIA), autonomic function (blood pressure, heart rate), and potential metabolic markers (cortisol, LCn-3 fatty acids, adiponectin, leptin, insulin and fibroblast growth factor-21) known to be regulated by sympathetic activity as predictors of response. This will be the first pilot study to evaluate the potential antidepressant effects of tsDCS in adult patients diagnosed with MDD. It is anticipated that the results of this pilot clinical trial will provide preliminary data in support of a larger future trial that will additionally incorporate neuroimaging to investigate central mechanisms.

A. SPECIFIC AIMS AND HYPOTHESIS:

Major depressive disorder (MDD) is a recurrent and often chronic mood disorder that affects 14 % of the adult population during their lifetime (1). MDD seriously undermines an individual's potential by reducing the ability to function, quality of life, increasing suicide risk, morbidity, mortality, and health related cost (2). Current therapeutic options used to treat MDD are effective in only a portion of patients and new treatment alternatives are urgently needed.

Mood can be viewed as the subjective experience that results from the integration of corporeal sensory input travelling through the spinal cord (lamina I) and the vagus nerve which convey spinal and parasympathetic information, respectively (3) to the nucleus of the tractus solitarius (NTS) in the brainstem. This information is then relayed to the thalamus and finally to the insula, where it is interpreted in a process called interoceptive awareness (4). This process allows human awareness of homeostasis and a cinemascopic version of emotional experience (5, 6). Thus, interoceptive awareness is an essential part of mood and seems to play an important role in MDD (7).

The brain uses the information gathered from the body to adjust corporeal function through hypothalamic and autonomic outputs (8). During a depressive episode, patients experience autonomic dysregulation suggesting that the sensory input to the brain might be disturbed and play a role in the pathogenesis of MDD (9). Specifically, increased sympathetic tone is associated with depression (10), and there is evidence that a sympathetic block (11) or drugs which affect sensory input to the brain have an antidepressant effect (12). Currently invasive and non-invasive neuromodulation treatments for depression exist in the form of transcranial magnetic stimulation (TMS)(13), transcranial direct current stimulation (tDCS)(14), deep brain stimulation (DBS) and vagal nerve stimulation (15). However, their effectiveness, risk, cost and limited device portability limit their widespread clinical application.

Spinal cord stimulation (SCS) has been safely and effectively used to treat pain syndromes for decades (16). Because of its sympatholytic effect, SCS has been widely used to treat peripheral vascular disease(17) and angina(18). Clinical trials of SCS in these conditions provide preliminary evidence for benefits of SCS in depressive symptom outcomes (19-23); an effect that has been shown to occur independent of pain reduction (22, 23). However, in these trials depression and psychopathology were exclusionary and the potential antidepressant effects of SCS have not yet been systematically studied in MDD patients (24, 25). There is therefore a significant knowledge gap regarding the efficacy of SCS for the treatment of MDD, and addressing this gap may provide an innovative approach for treating MDD.

Anodal transcutaneous spinal direct current stimulation (tsDCS) devices are available for investigational use and represent a low cost, non-invasive alternative to surgically implanted spinal cord stimulators. We therefore believe that extant data support our overarching **HYPOTHESIS** that an altered sensory input to the brain through the dorsal horns of the spinal cord contributes to the pathophysiology of depressive symptoms and that tsDCS will be effective and safe in

treating MDD by modulating spinal input to the brain, decreasing sympathetic activity, and restoring metabolic function as a consequence. As an initial test of our hypothesis, we will combine the use of a tsDCS device, psychometric instruments to diagnose MDD, and measures of depressive symptom severity, anxiety and somatic symptoms, interoceptive awareness, autonomic function, and possible metabolic markers known to be regulated by sympathetic activity as predictors of response. Additionally, adverse events will be documented to evaluate safety and tolerability.

Specific Aim 1: To determine the efficacy and safety of tsDCS in patients diagnosed with MDD. Prediction 1: Active tsDCS treatment will result in a greater decrease in depressive symptom severity (MADRS) compared to sham tsDCS in adult patients with MDD. Prediction 2: Active tsDCS will be safe and well tolerated in adult patients with MDD.

Specific Aim 2: To investigate interoceptive awareness, anxiety and somatic symptoms, autonomic and metabolic regulation as potential mediators of antidepressant response to tsDCS. Prediction 3: Change in interoceptive awareness, somatic symptoms, and autonomic and metabolic parameters will be associated with change in depressive symptom severity. Prediction 4: Active tsDCS treatment will result in a greater decrease in depressive symptom sub-components, interoceptive awareness, anxiety and somatic symptoms, autonomic and metabolic parameters.

To accomplish these aims, we will randomize 20 adult antidepressant-free MDD patients to active (n=10) or sham (n=10) tsDCS protocols for 8 weeks in a double blind 1:1 ratio. We will evaluate clinical, autonomic, and metabolic variables that may be involved in the proposed mechanism as possible mediators of antidepressant response. This will be the first 8-week, double blinded, randomized, sham controlled, parallel group pilot clinical trial to evaluate the efficacy and safety of tsDCS in adult patients with MDD. It is anticipated that the results of this pilot trial will provide preliminary data in support of a larger future trial that will additionally incorporate neuroimaging to investigate central mechanisms.

B. BACKGROUND AND SIGNIFICANCE:

B.1 Public Health Significance:

Major depressive disorder (MDD) is a highly prevalent and recurrent neuropsychiatric disorder that affects millions of people worldwide (26). In the United States, it is estimated that 14% of the population will suffer MDD during their lifetime (1). Mental disorders represent a leading cause of years lived with disability worldwide and depressive disorders account for 40% of disability adjusted life years caused by mental disorders (26). MDD impairs ability to function and increases suffering, suicide risk, metabolic comorbidity, cardiovascular risk, morbidity/mortality and health care costs (2, 27, 28). Current antidepressant medication effectiveness is variable and benefits only a portion of patients with small to moderate effect sizes and low response and remission rates (29-32). Other available treatments for depression, such as adjunctive medications (33, 34) and invasive or non-invasive neuromodulation (14), also show limited efficacy. Of note, current antidepressant strategies differ in their putative mechanism of action, but overlap in their targeted central neuropathological processes (antidepressant response). The neurobiological origin of depression and thus the targets for specific treatment remain elusive. *It is estimated that treatment with currently available antidepressants alleviates less than half the burden of MDD (35). Hence, MDD is a significant public health problem and there is an urgent need to*

advance our understanding of the neuropathophysiology of MDD and guide the development of new treatment alternatives. Our study could offer both a novel, low cost, non-invasive neuromodulation treatment and a confirmation of an extra-cerebral component in MDD. Results could also generate a new research pathway for the development of novel treatments for MDD, other psychiatric disorders as well as their medical comorbidities.

B.2 Brain-Body communication in the context of mood.

Over the past three decades, empirical evidence has grown to suggest that bi-directional brain-body communication is an essential component of emotional experience (3-5, 36-38). However, we still lack an integrative model that includes this knowledge in the context of mental health and the treatment of psychiatric disorders.

Our brain communicates with the body through neural and non-neural mechanisms that form a self-regulating circuit. For example, the hypothalamus is a complex neurological entity that represents just 0.3% (4cm^3) of the adult brain, but is a key region to understand brain output to the body. It controls systems essential in many physiological, endocrine and behavioral processes, including, among others, sleep/wake cycles, reproductive behavior, metabolic and cardiovascular regulation (39). These processes are tightly linked to higher cortical functions such as emotional regulation, fear responses, executive function, memory and pain and sensory perception that allow brain-body organization. The hypothalamus uses several pathways to communicate with the body through the outgoing hormonal and autonomic signals that need to be adequately synchronized in order to maintain homeostasis. Autonomic signals prepare the organs of the body for the coming hormones associated with the time of the day, moment for the reproduction cycle, feeding status and temperature. The hypothalamus not only modulates pre-autonomic neuronal systems connected to sympathetic and parasympathetic motor nuclei in brain stem and spinal cord, it also has hormonal 'motor' neurons able to release their content in the circulation. In addition, the hypothalamus receives information from the body about the level of metabolites and hormones, blood pressure and the physiological state of organs and is richly connected to the cortex. Via these elaborate pathways, the hypothalamus maintains a balance for optimal functioning of brain and body and deleterious consequences occur if this balance is lost or changed (8).

The communication between hypothalamus and body is bidirectional in order to maintain physiological balance (5, 40, 41). Somatic and sensory visceral information travels through the spinal dorsal horn (lamina I) and nucleus of the tractus solitarius (NTS), which convey spinal and parasympathetic information respectively to the thalamus (3). The thalamus sends the relevant information to cortical areas including the insula, providing consciousness of the corporal situation in a process called “interoceptive awareness” (4). At this level, the organization of information appears to be asymmetrical, with parasympathetic fibers signaling the left posterior insula, and spinal fibers to the right posterior insula (3). Although evidence regarding how the information is gathered and lateralized from the body and sent to the insula in “emotions” is currently limited, insular activity lateralization in emotional processing has been confirmed (42). Information next travels to the medial insula where the process of interoceptive awareness takes place and forms a cinemascopic version of emotional experience; this is essential for emotional processing and regulation as well as other cognitive processes such as motivational behavior and decision-making (5, 43). The NTS information is also sent directly to the hypothalamus

which acts accordingly to react or adapt bodily functions, and also sends and receives information to and from the prefrontal cortex (44). **(Figure 1)** This complex neuronal crosstalk between body and brain is essential for emotions, fear responses, circadian organization, feeding and sexual behavior, blood pressure and temperature regulation, as well as energy metabolism (8).

We view mood as the subjective experience that results from the integration of corporeal sensory input travelling through the spinal cord and NTS to the thalamus and then to the insula providing interoceptive awareness; which allows human awareness of homeostasis and the cinemascopic version of emotional experience (4, 5). Under physiological conditions, signaling from the body to the brain would result in harmonious feedback to the hypothalamus and appropriate modulation of bodily functions via the autonomic nervous system and contribute to a euthymic mood. Consequently, disturbed signaling from the body to the brain or from the brain to the body could alter physiology and influence mood.

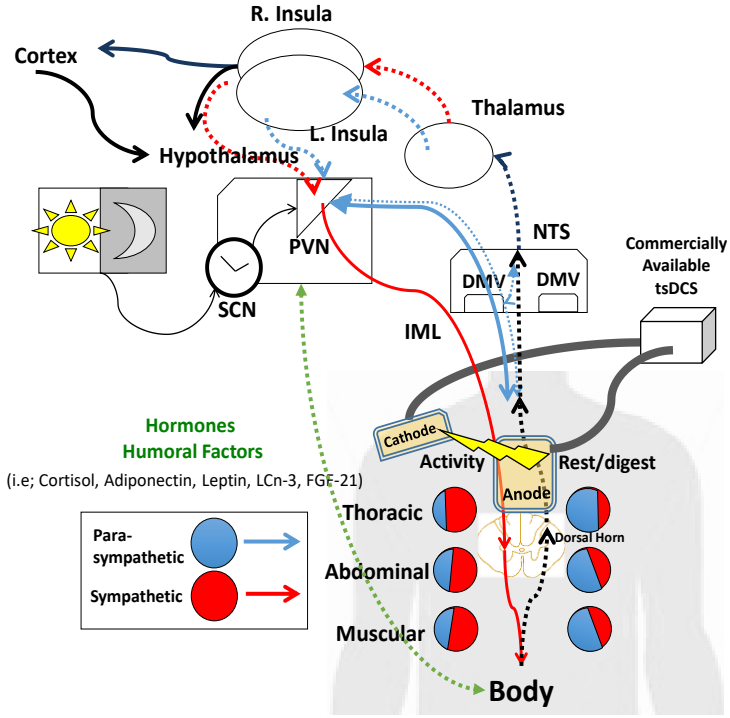

Figure 1. Shows brain-body communication pathways. Light/dark cycles and food are among the biological signals that synchronize our brain and body physiology in activity / rest and digest periods corresponding to day/ night demands. The biological clock in the suprachiasmatic nucleus (SCN) of the hypothalamus signals the pre-autonomic neurons in the paraventricular nucleus (PVN) to adjust the physiology through the parasympathetic branch of the autonomic nervous system via the dorsal motor nucleus of the vagus (DMV) and the sympathetic branch through the intermediolateral column (IML) to target organs. Visceral and somatic information travels back to the brain through the vagus and nucleus of the tractus solitarius (NTS), the lamina I in the dorsal horn of the spinal cord to the thalamus and then to the Right (R) and/or Left (L) insula. Continuous arrows show efferent pathways; dashed arrows show afferents. .Another feedback between body and brain is through hormonal and humoral factors (green).

B.3 Disturbed brain-body communication in MDD: MDD is strongly associated with stress, circadian rhythm disruption (45) and other environmental and genetic factors. It is characterized by a cluster of symptoms that include not only a low, sad or irritable mood, but also decreased attention and motivation, self–defeating and suicidal thoughts, and disturbance of other cognitive domains, sleep, appetite and sexual interest (46). Additionally, anxiety, pain and other somatic complaints are present in more than half of patients experiencing MDD (47). MDD is often recurrent (48) and/or chronic (49). To date, maybe the most consistent evidence of brain-body communication disruption in MDD has been reported in the form of direct or indirect measurements that indicate autonomic disturbance.

B.3.1. Increased sympathetic activity and disturbed metabolism in MDD. There is now a substantial body of evidence showing disturbed autonomic nervous system function in MDD. The evidence shows that the stress response system involving the hypothalamic-pituitary-adrenal axis and the sympatho-medullary system is hyperactive before, during and after depressive episodes (50). Evidence of such hyperactivity can be observed in the form of increased cortisol (51) and leptin (52), as well as decreased adiponectin (53) levels in patients with MDD. Cortisol, adiponectin, leptin and fibroblast growth factor-21 (FGF-21) levels are a reflection of the autonomic output from the brain to the body; particularly sympathetic tone (54), which is also regulated by the biological clock located in the suprachiasmatic nucleus of the hypothalamus (8, 55-57). LCn-3 fatty acids also play an important role in brain-body communication and are involved in regulating circadian, and autonomic function (58, 59). LCn-3 have been implicated in the pathophysiology and antidepressant treatment response of MDD (60). It has also been reported recently that the metabolic hormone FGF-21, which is mainly produced by the liver, is an important signal for biological clock regulation (55) and it is largely driven by sympathetic tone (61). It is unknown whether FGF-21 levels are changed during a depressive episode and if this levels could inform on the status of brain-body communication in MDD. Circadian cortisol release by the adrenal gland greatly depends on sympathetic tone under the control of the biological clock and not entirely on ACTH release (57). This could help explain why the dexamethasone suppression test failed as a diagnostic tool and as a reliable predictor of treatment response for MDD patients (62). Increased cortisol level in MDD is often interpreted as a cause of MDD (63), but instead could be a consequence of other phenomenon such as a disturbed brain-body communication, such as increased sympathetic tone. Increased sympathetic activity has also been documented in MDD patients in the form of decreased heart rate variability (64, 65), which is inversely correlated with depressive symptom severity (66, 67). It is therefore not surprising that MDD patients show increased comorbidity with obesity (68), metabolic syndrome (69) and diabetes (70), all of which are associated with increased sympathetic tone (71). *Taken together, this evidence suggests an important role of the autonomic nervous system and disturbed brain-body communication in the pathophysiology of MDD that could also explain the increased cardiovascular risk of this disorder* (28, 72). It further suggests the possibility that levels of metabolic markers such as cortisol, adiponectin, leptin, and FGF-21 are disturbed during MDD as a consequence of increased sympathetic activity. If correct, decreasing sympathetic activity would be anticipated to reduce depressive symptoms, as well as to "normalize" metabolic risk biomarkers.

B.3.2. Spinal cord stimulation (SCS), depressive symptoms and metabolism. Given its sympatholytic effect, SCS has been used to treat a variety of conditions associated with increased sympathetic tone, including peripheral vascular disease (17) and angina (18), but has not been directly studied for MDD treatment. The most widely used SCS application is chronic pain (73), a condition frequently comorbid with depression (47). Among the trials published on SCS as an effective treatment for pain, a few report on depressive symptom change. *Interestingly, SCS trials that report specific depression outcomes show an improvement in depressive symptom severity (21-23, 74). At least two trials have shown no correlation between the effect of SCS in pain and depressive symptom improvement (22, 23).* Of note, a decrease in depressive symptom severity was observed even when severity was mild. This is important, as clinical

depression in the form of MDD was usually an exclusion criterion for participation in such trials. Remarkably, a study on the effects of thoracic sympathetic block also showed a decrease in depressive symptom severity (11). Recently, although applied at a cervical level, SCS was successfully used to decrease weight in morbidly obese patients by decreasing sympathetic activity and increasing parasympathetic activity (75). A recent study in rodents recently showed that spinal injury induced a long lasting depressive and anxious phenotype, underscoring the potential role of spinal function in the pathophysiology of depression and anxiety (76).

In our view, these results suggest a role for brain-body communication in the pathophysiology of MDD and an unexplored antidepressant effect of SCS that is independent from the effect in pain. Such antidepressant effect could be mediated through a decrease in spinal input from the spinal cord to the brain (via the dorsal horn) and/or from brain sympathetic output to the body (via the intermediolateral column). Additionally, SCS could improve, cardiovascular and metabolic function through its sympatholytic effects. **(Table 1)**

Table 1. Spinal cord stimulation trials for the treatment of pain with reports on mood improvement.

Author	Year	SCS (protocol)	Design (n)	Reported outcome
Burchiel KJ	1995	SCSQx	Prospective 3 month follow up (40)	BDI Pre>Post. No correlation % Change in pain and BDI change
Burchiel KJ	1996	SCSQx	Prospective 1 year follow up (70)	BDI Pre>Post. No correlation % Change in pain and BDI change
Jamison RN	2008	SCSQx	Cross-sectional (273)	HADS SCS<No SCS.
Wolter T	2013	SCSQx (SCS for average 4.8 yrs) Most Thoracolumbar	Retrospective (60)	HADS. Dep Pre>Post.
Kumar K	2008	SCS Qx	Prospective 2 year follow up (42)	Mental health and QoL improved
De Oliveira Rocha R	2014	Thoracic Sympathetic block	Prospective 1 year follow up (29)	HADS. Dep Pre>Post.

Beck Depression Inventory (BDI); Hospital Anxiety and Depression Scale (HADS); Quality of Life (QoL)

B.3.3. Transcutaneous spinal direct current stimulation (tsDCS) as a non-invasive neuromodulation alternative for surgically implanted spinal cord stimulators. SCS studies have focused on an invasive SCS modality using a device that is implanted surgically. This is an effective, but invasive and expensive option for spinal cord stimulation. Spinal cord stimulation can also be achieved effectively, safely and at a lower cost through tsDCS (77). Preliminary data shows that tsDCS promotes locomotor learning with long lasting effects after only three SCS sessions (Awosika O, personal communication). **(Figure 2)** Anodal tsDCS can inhibit ascending (78-80) and descending (81) spinal pathways. This is consistent with the evidence showing that SCS decreases sympathetic tone, which could be explained by an inhibitory effect at the intermediolateral column (IML) or at ascending spinal pathways in the dorsal horn.

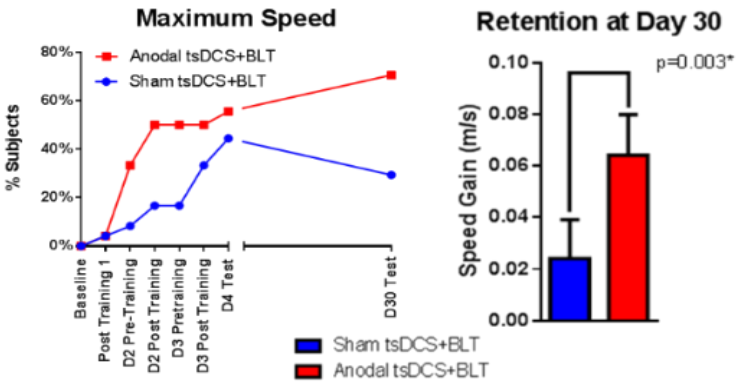

Figure 2. Shows tsDCS effects in locomotor training.

A resting state fMRI study with a double blind and cross-over design, recently showed that anodal tsDCS at the T11 spinous process at an intensity of 2.5 milliampere (mA) for 20 min resulted in a decreased connectivity between the primary somatosensory cortex and the ipsilateral posterior insula for both left and right hemispheres. Anodal tsDCS also induced decreased thalamic connectivity with the anterior cingulate cortex and increased connectivity between the primary somatosensory cortex and the thalamus (82). We interpret these results as evidence of supraspinal effects of tsDCS and its potential to target and modify function in mood related brain regions such as the insula.

Neuromodulation through tsDCS is still an emerging technology. Several stimulation protocols have been studied to date. For example, at the cervical level and using an anterior-posterior anodal stimulation, tsDCS at 3 mA during 20 min was well tolerated, but showed no effect on descending motor pathways at cortical, spinal or motor neuronal levels, and did not change efferent components of the H-reflex pathway (83). This suggests that tsDCS, even at the cervical level, is safe and does not affect motor pathways at an intensity of up to 3.0mA.

B.4 Summary.

We believe that the available evidence supports our overarching HYPOTHESIS that a disturbance in brain-body communication in the form of increased sympathetic activity and altered spinal input to the brain is involved in the physiopathology of MDD and that tsDCS represents a non-invasive tool to decrease sympathetic activity and modulate spinal input to the brain in order to improve depressive symptom severity, while improving metabolic function. It is therefore anticipated that patients with MDD treated with active tsDCS will show a greater decrease in depressive symptom severity compared to those receiving sham tsDCS. Further, we expect that the modulation of sympathetic activity through tsDCS will also modify clinical, autonomic, and metabolic parameters that could serve as evidence of target engagement of the proposed brain-body circuit and markers of antidepressant treatment response.

C. INNOVATION.

There is an urgent and unmet need for new and efficacious antidepressant treatments and to improve the understanding on the physiopathology of MDD. We will conduct the first pilot randomized controlled clinical trial to test the efficacy and safety of tsDCS for the treatment of MDD. In addition to providing evidence of a potentially new treatment alternative for depression, we expect that our findings will aid in confirming the involvement of extracerebral neural pathways in the physiopathology of MDD and provide novel biomarkers influenced by such pathways and possibly in response to treatment. In addition, our findings are anticipated to provide the foundation for a new research avenue for the development of neuromodulation strategies to treat other mental disorders such as bipolar disorder, anxiety disorders, ADHD and their non-psychiatric medical comorbidities for which the proposed mechanisms may also be involved. Within the framework of Research Domain Criteria (RDoC) the present proposal entails the *perception and understanding of Self in the sub-construct of Agency*, as well as the domains of *Arousal/Regulatory systems and Circadian Rhythms*. Our proposal also responds to the Strategic Plan for Research set for by the National Institute of Mental Health **objective 1)** Define the mechanism of complex behaviors in its *priority for strategy 1.1.D.2: Investigating*

the role of coordinated neural activity in normal cognitive, affective and social processes, and aberrant functions in mental illnesses; and **objective 3**) *Strive for prevention and cures, in its priority for strategy 3.1.A.2: Developing treatments that target specific neural or psychological systems critical for core domains of cognitive and emotional function relevant to mental illness* and *priority for strategy 3.1.C.2: Developing validated proxy measures or markers that are relatively brief and inexpensive for use in multi-modal assessments in outcomes research.*

D. APPROACH

D.1 Study Overview.

This is a study with a double-blinded, randomized, parallel group, sham controlled pilot clinical trial design. The protocol will be submitted to the Institutional Review Boards of the University of Cincinnati for review and approval. *This is a joint effort among basic and clinical researchers at the Lindner Center of Hope (a University of Cincinnati College of Medicine affiliate), the Department of Psychiatry and Behavioral Neuroscience and the Department of Neurology and Rehabilitation Medicine at the University of Cincinnati College of Medicine.*

Participants. Subjects will be recruited from the community and from the Lindner Center of Hope through advertising and word of mouth. *Location:* All study procedures involving participants will be conducted at the Lindner Center of HOPE. *Inclusion criteria*: 1) age 18-55 yrs., inclusive; 2) female or male; 3) BMI 18.5 to 35 kg/mts^2, inclusive; 4) current MDD episode diagnoses confirmed by Mini International Neuropsychiatric Interview (MINI) 5.0 with a duration of ≥1 month and ≤24 months; 5) moderate MDD symptoms according to Montgomery-Asberg Depression Rating Scale (MADRS) score ≥ 20 to ≤35; 6) no current or recent (past month) antidepressant pharmacological treatment; 7) GAD and other anxiety symptoms will be permitted; 8) using an effective contraceptive method (all participants of childbearing potential). *Exclusion criteria*: 1) Current or lifetime MDD episode non-responsive to two or more antidepressant treatments at adequate doses and time (including ECT); 2) Current or lifetime bipolar disorder or schizophrenia diagnosis; 3) current (past month): PTSD, psychotic or substance use disorder (nicotine and caffeine allowed); 4) significant risk of suicide according to CSSRS or clinical judgment, or suicidal behavior in the past year: 5) current chronic severe pain conditions; 6) current chronic use of: opioids analgesics, medications that affect blood pressure or drugs with significant autonomic effects (stimulants and antipsychotics allowed if dose stable for 1 month); 7) neurological, endocrinological, cardiovascular (including diagnosed hypertension) or other clinically significant medical conditions as judged by the clinician; 8) skin lesions on electrode placement region; 9) implanted electrical medical devices; 10) Pregnancy; 11) suspected IQ<80, and 12) any other clinically relevant reason as judged by the clinician.

D.1.1. Psychometric evaluations. The Mini International Neuropsychiatric Interview 5.0 (MINI)(84) will be used to confirm the diagnosis of current MDD and evaluate the presence of comorbid psychiatric disorders. The Montgomery-Asberg Depression Rating Scale (MADRS)(85) will be used to evaluate depressive symptom severity and the Columbia Suicide Severity Rating Scale (CSSRS)(86) will be used to evaluate suicidality. The clinical global impression- severity (CGI-S) and the clinical global impression-improvement (CGI-I) scales will be used to evaluate the overall clinical severity and

improvement of the illness (87). Participants will also complete self-report instruments including the Patient Health Questionare-9 (PHQ-9) as an additional measure of depressive symptom severity(88). The Four-Dimensional Symptom Questionnaire (4DSQ)(89) to measure distress, somatization and anxiety symptoms, the Binge Eating Scale (BES) to measure eating behaviors and aspects of body perception(90) and the multidimensional assessment of interoceptive awareness (MAIA) as a quantitative measure of interoceptive awareness (91). Participants will complete an electronic version of the emotion recognition task (92, 93) and the stop signal task (94, 95) prior to tsDCS (offline) and during tsDCS (online) in order to obtain preliminary data on the effect of tsDCS on emotion recognition and cognitive function. A paper, electronic and/or a REDcap electronic version of the instruments may be used to complete the psychometric evaluations.

D.1.2. Spinal cord stimulator and stimulation protocol. The 2x2 Soterix® Medical transcutaneous spinal direct current stimulator model 0707-A device will be used. This is a tsDCS available only for investigational use, with which Dr. Awosika has extensive experience and will provide appropriate training to the study team. This device will be appropriately labeled as an "Investigational Device. Federal (Law) limits device to investigational use". The device will be kept in a secured area inside the LCOH Research Institute and will be made available only to trained personnel of the study team. This device allows anodal stimulation to be delivered at 2.5mA per 20-minute session or sham session consisting of short pulses (of the desired intensity) at the beginning and end of the sessions. This protocol of anodal stimulation has been reported to be effective in inhibiting ascending pathways with a lasting effect, to be safe and well under the threshold for tissue damage (77, 79). If stimulation intensity (in active or sham protocols) is not tolerable at 2.5mA, the clinician may decide to decrease intensity to 2.0 mA or 1.5 mA. If 1.5 mA stimulation intensity is not tolerated, the subject may be withdrawn from the study. If subject has tolerated a stimulation intensity of less than 2.5mA, the study clinician may attempt to increase the dose to 2.0mA or 2.5mA when considered clinically appropriate. An anode electrode (5x10cm) will be placed at the level of the 10^{th} vertebrae spinal process. At this level, the current is expected to spread longitudinally through the spinal cord up to three additional vertebral levels (96). The cathode (5x7cm) electrode will be placed on the right shoulder over the deltoid area (78, 79, 97). Participants will be scheduled to receive sham or active tsDCS sessions three times/week. Subjects will be randomized in a 1:1 ratio using a simple allocation method to one of two experimental groups: 1) sham or 2) stimulation protocol. Randomization will be double-blinded. An independent operator (trained personnel from the research team) will prepare the tsDCS device parameters for each session, but will not participate in the rest of the assessments. Patients and raters will remain blinded to SCS protocol assigned to each participant throughout the study. During the session, subjects will remain in a calm and relaxing environment. All participants will be scheduled for the same procedures and number of scheduled visits during the eight-week follow-up period. **(Table 2)**

D.1.3. Blood and urine samples. *General*: *Blood samples (approximately 20ml per occasion) will be obtained on visit 0 and 6* for a) Hematology: Complete blood count (CBC); b) electrolytes; c) liver panel; d) kidney panel; e) lipid panel; f) other: glucose and TSH. A urine sample *for* urinalysis will be collected at screening*. A serum human chorionic*

gonadotrophin (HCG) determination (blood pregnancy test) will be conducted at visit 0, visit 4 and 6 (if applicable). Blood sample processing for these tests and urinalysis will be performed at Quest Diagnostics. *Special focus metabolic markers*: *Blood sample (approximately 5ml per occasion) will be obtained on visit 1, 4 and 6* for: Adiponectin, leptin, cortisol, insulin and FGF-21 levels. Samples will be processed using ELISA assays at the Biochemistry Core Laboratory from the Schubert Research Clinic at Cincinnati Children's Hospital. A blood sample (approximately 5ml per occasion) will be obtained for Fatty acid analyses: Patients (N=20) will have their blood fatty acid composition determined by gas chromatography at visit 1, visit 4, and visit 6 at no cost by the Lipidomics Research Program which is Directed by Dr. McNamara (Co-Investigator).

D.1.4. Cardiovascular measurements. Blood pressure will be obtained before and after SCS sessions through the auscultatory technique using a standard mercury sphygmomanometer in a sitting position after 5 minutes of rest. An ECG tracing will be obtained through standard 12-lead electrocardiography at visit 0, 1, 4, and 6. For the purpose of this study, we will consider blood pressure and heart rate as variables to assess cardiovascular autonomic function.

D.1.5. Anthropometric measures. Height will be obtained at screening. Weight, Waist and abdominal circumference and Body Mass Index (BMI) will be measured on visits 0, 1, 3, 4, 5 and 6.

D.2. Protocol visits.

Visit 0 (Screening). Subjects will be informed about study procedures and given a written informed consent to sign voluntarily before any study procedure is initiated (See Informed consent form attached to this protocol). Then, the clinical staff will evaluate the participant in order to obtain a psychiatric and medical history. The MINI will be used to confirm MDD diagnosis, the MADRS to evaluate depressive symptom severity and the CSSRS for suicidality. The clinical research team will perform a full neurological and physical evaluation, ECG, cardiovascular measurements, laboratory tests, urinalysis, urine drug test, and a blood pregnancy test (if applicable). After eligibility is confirmed, a baseline visit will be scheduled.

Visit 1 (**Baseline).** After verification of eligibility, subjects will be randomized to an "active" or to a "sham" tsDCS protocol. Treatment allocation will remain double-blinded throughout the study to raters and study physicians. A MADRS, CGI-S, CSSRS, PHQ-9, 4DSQ, BES and MAIA will be completed. BMI, waist and abdominal circumference, vital signs, blood sample and ECG will be obtained. A physical and neurological evaluation will be conducted. Participants will complete the ERT and SST prior and during the SCS protocol. Each participant will receive the assigned SCS protocol.

SCS sessions (1-24): Three tsDCS sessions per week will be scheduled. A CSSRS will be completed before each SCS session. Blood pressure and heart rate will be evaluated prior and after each tsDCS session. AE's will be assessed after each session through open-ended questions.

Full visits 2, 3, 4, and 5: A MADRS, CSSRS, CGI-S, CGI-I, PHQ-9, 4DSQ, BES and MAIA scales will be completed. Anthropometric measures (Visit 3, 4, 5), vital signs, and ECG (Visit 4) will be obtained. A blood sample (visit 4), urine drug test (Visit 4) and pregnancy test will be performed if applicable (visit 4). A physical and neurological evaluation will be

conducted (Visit 3, 4, and 6). Participants will complete the ERT and SST prior and during the SCS protocol (Visit 4). Each participant will receive the respective tsDCS protocol. AE's will be recorded after each tsDCS session.

Full Visit 6 (Final visit): A MADRS, CSSRS, CGI-S, CGI-I, PHQ-9, 4DSQ, BES and MAIA scales will be completed. Anthropometric measures, vital signs, blood sample, pregnancy test and ECG will be obtained. A drug urine test will be performed. Participants will complete the ERT and SST prior and during the SCS protocol. Each participant will receive the respective tsDCS protocol. A physical and neurological evaluation will be conducted. AE's will be recorded after each tsDCS session.

Table 2. Schedule of events

	Screen Visit 0 (Day -14 +/- 7)	Baseline Visit 1 (Day 0)	Visit 2 Day 7 +/-4)	Visit 3 (Day 14 +/- 4)	Visit 4 (Day 28 +/- 4)	Visit 5 (Day 46 +/- 4)	Final Visit Visit 6 (Day 56 +/- 4)
MINI	X						
MADRS	X	X	X	X	X	X	X
PHQ-9,		X	X	X	X	X	X
CGI-S & CGI-I, 4DSQ, BES and MAIA.		X	X	X	X	X	X
ERT and SST		X			X		X
CBC, LFT, Renal, Lipid, Glucose and TSH.	X						X
Urinalysis	X						X
Serum HCG	X	X			X		X
Drug Urine test.	X				X		X
Adiponectin, FGF-21, Leptin, LCn-3, Insulin, Cortisol		X			X		X
Anthropometric measurements	X	X		X	X	X	X
EKG	X	X			X		X
Physical and Neurological Evaluation	X	X		X	X		X

	Screen	Baseline			Week 1			Week 2			Week 3			Week 4			Week 5			Week 6			Week 7		Final Visit
tsDCS sessions		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CSSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Pressure*, HR*		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Complete Blood Count (CBC); Liver Function Test (LFT); Thyroid stimulant hormone (TSH); Fibroblast Growth Factor-21 (FGF-21), Long Chain fatty acids (LCn-3), Heart Rate (HR), Electrocardiogram (EKG). Emotion recognition task (ERT) and the stop signal task (SST) to be completed prior and during the corresponding tsDCS sessions.
*Measured pre and post tsDCS session.

Menstrual phase will be documented at each full visit. Participants will be referred for aftercare after study completion with their primary care physician (PCP) or will receive referral information for a psychiatrist or other mental healthcare professional. Participants will be compensated with a total of up to $250 ($10 per visit) for their time and effort through a prepaid debit card. Subjects are expected to attend to the Lindner Center of Hope a total of 25 times. Free parking is provided. Additional unscheduled visits may be arranged if needed. Full visits may be scheduled with a window of +/- 4 days. A participant may not be allowed to continue on the study if the participant misses more than 6 consecutive tsDCS sessions or has missed more than 8 tsDCS sessions on separate occasions.

D.3. Participation of human subjects.

This study will be performed in compliance with International Conference of Harmonization (ICH) Good Clinical Practice (GCP) and corresponding local regulations. Participation will be voluntary; subjects will be informed in detail about the

study, including potential risks and benefits of participating and will agree to participate by reading and signing an informed consent (See informed consent form attached to this protocol). The informed consent form will be written in a language that is understandable for potential participants. The study team will be available to answer any questions before the potential participant decides to sign the informed consent form. All required study documentation will be confidential and archived as required by regulatory authorities. *Data and Safety Monitoring Plan*: This plan will include monitoring of efficacy and safety data by an independent Data Safety Monitoring Board (DSMB) that will meet every six months and will provide oversight and monitoring to ensure the safety of participants and the validity and integrity of the data. Detailed information on the Data and Safety Monitoring plan and DSMB is contained in *Protection of Human Subjects* section of this protocol.

E. OUTCOMES

Primary Outcome: Difference in change from baseline to week 8 (or last available observation) in MADRS scores between active and sham tsDCS groups. **Secondary Outcome: a)** differences in AE's frequency between active and sham tsDCS groups, **b)** association between change from baseline to week 8 (or last available observation) in MADRS scores, and clinical (CGI-I, CGI-S, PHQ-9, MAIA, BES and 4DSQ), autonomic (BP, HR) and metabolic (anthropometric, adiponectin, leptin, cortisol, FGF-21 and LCn-3) parameter change from baseline to week 8(or last available observation), and **c)** MADRS sub-component (98) scores, clinical parameters (CGI-I, CGI-S, PHQ-9, MAIA, BES and 4DSQ), autonomic (BP, HR), and metabolic (anthropometric, adiponectin, leptin, cortisol, insulin, FGF-21 and LCn-3) parameters change from baseline to week 8 (or last available observation) difference between Active and Sham tsDCS groups. **Exploratory outcome measures: a)** difference in change from baseline to week 8 (or last available observation) in offline ERT and Stop signal task scores between active and sham tsDCS groups; and **b)** difference in change from baseline to week 8 (or last available observation) in offline and online change ERT and stop signal task scores between active and sham tsDCS groups

F. SAFETY MEASURES

Potential Risks. Safety evaluation will consist in recording all laboratory tests, vital signs and ECG results, suicidality monitoring (each SCS session), physical and neurological examinations and any adverse events (AE). As mentioned above, literature suggests that current density below 25 mA/cm^2 induces no tissue damage (99). Findings will be recorded as AEs at the discretion of the investigator. Known side effects to tsDCS are paresthesia, redness, itch, or pain in stimulated area. If they occur, these side effects tend to disappear within minutes to hours after stimulation. To our knowledge, no serious adverse effects have been reported with the use of transcutaneous direct current stimulation protocols using $2.5mA/cm^2$ (100).

Risk/Benefit Assessment. Participants will be informed that there are other FDA approved treatment alternatives for major depressive disorder and that their participation in this study is voluntary. Therapeutic options include antidepressant medications, psychotherapy, invasive and non-invasive neuromodulation tools. Participants will also be

informed that tsDCS is an investigational technique that has been used in humans for other purposes, but this study will be the first to explore tsDCS as a potential treatment for major depressive disorder. It is expected that tsDCS will be effective and safe in treating depressive symptoms, while improving other aspects of brain-body communication as indicated by improvement in interoceptive awareness, anxiety and somatic symptoms, autonomic, and metabolic parameters.

Adverse events. As defined by the ICH and GCP guidelines, any untoward medical occurrence in a patient during the administration of the investigational procedure and which does not have a causal relationship with treatment will be considered an AE.

Early withdrawal. A subject may voluntarily decide to end participation at any point during the study. Clinical investigators may decide to end study participation of any subject if it is in the best interest and/or safety of the subject. If at any point during the study a patient has a MADRS suicide item score > one point higher than their visit 1 (baseline) score for any one week, or a score of > 4; or active suicidal behavior on the C-SSRS; or appears to the investigator to pose a risk of self-harm or harm to others, the patient may be withdrawn from the study. Additionally, patients will be withdrawn from the study (and referred for treatment as clinically indicated) if there is a worsening of symptoms at visit 2 or later, as indicated by a CGI-I score of ≥ 6 or more at any time during the study or a minimal worsening of symptoms at visit 3 or later as indicated by a CGI-I score of ≥ 5 at 2 consecutive visits, starting at visit 2; or a 50% increase over baseline in total MADRS rating and a total MADRS> 28, at visit 3 or later. Patients will also be withdrawn from the study at week 3 or later if they demonstrate a ten-point increase from baseline in MADRS score for two successive weeks starting at visit 2. In addition, all patients will be assessed with the C-SSRS on every tsDCS session to elicit risks of potential suicidality. During study participation, a study related clinical investigator will closely monitor all study participants at each study visit for suicidal or homicidal ideation, plan, or intent using clinical interviews as well as the information obtained from rating scales. Transient suicidal ideation will not result in study discontinuation or referral for inpatient care since this may be common for patients with major depressive disorder. In order to maximize subject safety, if a subject exhibits active suicidal or homicidal ideation during study participation that, in the judgment of a clinical study investigator, cannot be managed on an outpatient basis, he/she will be withdrawn from the study and referred for inpatient psychiatric care. Patients with active suicidal behavior may be removed from the study based on C-SSRS criteria, as noted above. All subjects who discontinue study participation prior to visit 6 will be asked to voluntarily undergo endpoint study procedures, if feasible. Additionally, all study participants will be provided with study physician contact information and instructed to contact their study physician 24 hours/day, 7 days/week in between visits should suicidal or homicidal ideation or any other emergency situation occur. If a participant becomes pregnant during the study, participation will be stopped, and the event will be documented as a serious adverse event. The participant will be referred for appropriate medical treatment and follow up with primary care physician and followed by the study team throughout the pregnancy and the outcome documented as required by the IRB and institutional guidelines. We have successfully followed this protocol in our prior

outcome and clinical trials studies. A study physician will work with the patient to arrange admission in the event that it is determined that a study participant needs psychiatric or medical hospitalization.

G. SAMPLE SIZE.

This is an exploratory pilot clinical trial for which up to 60 (including screen fails) participants will be screened in an effort to recruit 20 participants that will receive either sham (n=10) or active treatment (n=10) for 8 weeks. Recruitment efforts will be aimed at a 2 patient/month rate. The exploratory nature of the study precludes a sample size that would enable detection of small but still clinically relevant effects at conventional significance thresholds. However, estimates of effect sizes with confidence intervals will be useful as inputs to larger confirmatory studies if these effects fall in an appropriate range (i.e., at least moderate sample effect sizes of approximately 0.50 standard deviations), even if the conventional significance is not achieved.

H. FEASIBILITY OF RECRUITMENT AND RETENTION

Resources and Infrastructure: The University of Cincinnati (UC) College of Medicine, Department of Psychiatry was founded in 1932 and UC is the 14th largest recipient of NIH funding. Among departments of Psychiatry, UC has one of the largest psychopharmacology research programs in the United States dedicated to depression and bipolar disorder. The faculty has a long-term successful record of sustained research support related to mood, eating, and impulse control disorders and pharmacological treatments.

The Lindner Center of HOPE (LCOH) is a nonprofit 91,820 square foot Mental Health facility affiliated with the University of Cincinnati and located in Mason, Ohio. LCOH provides comprehensive mental health, substance abuse, and dual diagnosis services. The Center was a founding member of the National Network of Depression Centers (NNDC), de facto recognition as a center of excellence in the treatment and research of mood disorders. The facility is located on 36 acres and is easily accessible to the Tri-state area (Ohio, Kentucky and Indiana). LCOH has 48 inpatient beds with separate units for adolescents, adults and elderly patients. The annual capacity is 1,400 inpatients and 29,000 outpatients. The facility treats patients with public and private health insurance. Onsite assets include: pharmacy, dining room, faith center, library, gymnasium, and exercise room. LCOH is accredited by The Joint Commission for Hospital and Behavioral Health Care, licensed as a Private Psychiatric Hospital by Ohio Department of Mental Health and Certified for Mental Health Services by Ohio Department of Mental Health.

The LCOH Research Institute located onsite is dedicated to conducting clinical, outcomes, and genetics research. The Research Institute has conducted numerous clinical trials of pharmacological treatments for mood, eating, and anxiety disorders. The Research Institute is staffed by 4 Psychiatrists, 1 PhD, 4 Research Assistants, 1 Nurse Practitioner, 1 Statistician, and has dedicated Administrative support. The Research Institute has two exam rooms equipped with an electrocardiogram and laboratory space equipped with a -80^{o}C freezer to store blood samples, centrifuge, phlebotomy equipment and other supplies for routine medical examinations. Dr. McElroy is the Chief Research Officer of the Research

Institute and Dr. Romo-Nava is Associate Chief Research Officer. PI Dr. Romo-Nava is a Psychiatrist with a PhD in Biomedical science and experience in non-invasive neuromodulation licensed to treat patients in Ohio. Co-I Dr. Awosika is a Neurologist with extensive experience on tsDCS in the context of neurological rehabilitation and will provide additional training to study staff on the use of the tsDCS device and any other associated technical aspects. The Clinical Staff at the LCOH Research Institute are trained in conducting numerous assessments including Structured and semi-structured clinical Interviews for DSM-IV and DSM-5 Axis I Disorders and Axis II Disorders, MINI and other psychometric instruments. The staff employed at the LCOH Research Institute has over 20 years' experience conducting research and recruiting study participants from the local environment (prior to LCOH opening the staff were part of the Clifton campus of the UC Department of Psychiatry).

Recruitment: The LCOH Research Program has access to a full-time marketing staff, which, in turn coordinates television, radio and newspaper advertisements after appropriate approval by the UC IRB. In addition to advertising, subjects are recruited from clinician referral and the LCOH intake department, and by marketing outreach personnel. UC and LCOH also have excellent technical resources (e.g., personal computers and software) for the analysis of data and preparation of manuscripts. Both PC and Macintosh computers are available and the Information Management staff at LCOH is experienced in a variety of database programming languages including Stata, SAS, and SPSS. LCOH has integrated cutting-edge technology including an electronic medical record; wifi that integrates computers, telephones and voicemail; and state-of-the-art protection of patient-identified electronic data. The LCOH IT staff has expertise in web development and already manages the LCOH website (www.lindnercenter.org) in coordination with the marketing department.

I. DATA MANAGEMENT AND ANALYSIS.

Data management and analyses will be organized and performed by the research team under the guidance of Dr. Jeffrey Welge, Director of the Division of Biostatistics in the Department of Psychiatry at the University of Cincinnati, who has participated in the development of this analytic plan. Data will be collected via Case Report Forms. The research coordinator will be responsible for managing the study flow, maintaining case report forms, and entry data into a password-protected database on REDcap.

Data Analysis. *Specific Aim 1*: *Prediction 1*) Active tsDCS treatment will result in a greater decrease in depressive symptom severity (MADRS) compared to Sham in adult patients diagnosed with MDD. *Efficacy:* Longitudinal effect of tsDCS will be assessed by comparing change in MADRS scores from baseline to week 8 (or last available observation). To take maximum advantage of intermediate observations while avoiding assumptions about the trajectory of change over time, we will use a repeated-measures ANOVA model (i.e., with time as a categorical variable), and the primary hypothesis test will be a planned contrast of the baseline-week 8 differences between groups. *Prediction 2)* Active tsDCS is safe and well tolerated in adult patients diagnosed with MDD. *Safety:* A similar analysis as used for efficacy data will be performed for laboratory assays, vital signs, anthropometric, clinical, autonomic and metabolic variables. Frequencies of AE's will be compared between groups using comparative analysis. *Specific Aim 2*: *Prediction 3)* Baseline and change in interoceptive awareness,

somatic symptoms, clinical, autonomic and metabolic parameters will be associated with change in depressive symptom severity. A correlation analysis will be used to evaluate the association between treatment and depressive symptom severity, both total and in components (items). Correlation analysis will also be performed by gender, autonomic and metabolic parameters. Prediction 4) Active tsDCS treatment will result in a greater change in interoceptive awareness, anxiety and somatic symptoms, clinical, autonomic and metabolic parameters. Longitudinal effect of tsDCS will be assessed by comparing MADRS sub-component scores, clinical parameters (CGI-I, CGI-S, PHQ-9, BES, MAIA, and 4DSQ), autonomic, and metabolic parameters change from baseline to week 8 (or last available observation) difference between Active and Sham groups using a repeated-measures ANOVA as described above. Throughout, tests and confidence intervals for effect sizes will be two-sided, α=0.05.

J. PROTECTION OF HUMAN SUBJECTS.

The data and safety monitoring plan for the proposed study will include monitoring of efficacy data by an independent Data Safety Monitoring Board (DSMB) and monitoring of tolerability data, including adverse events and serious adverse events, by the study investigators as well as the independent DSMB and the University of Cincinnati College of Medicine Institutional Review Board (IRB). The DSMB will consist of non-study related faculty with relevant research experience.

Data Safety Monitoring Board. In order to maximize the safety of the study participants, in addition to adverse event monitoring by study investigators, the proposed study will also have a Data Safety Monitoring Board (DSMB). The DSMB will consist of non-study related faculty with research related experience and will include a psychiatrist with expertise in clinical research and mood disorders (Fabbiano Neri, MD, PhD), a psychiatrist or neurologist with experience in non-invasive neuromodulation (Jonathan Cole, DO), and a researcher with experience in biostatistics or a biostatistician (Thomas Blom, MS). The DSMB members will not have a potential conflict of interest in study related outcomes. The DSMB will meet a minimum of every 6 months during the course of the study and will review tolerability, safety and efficacy data. The DSMB will also review all SAEs at the time of their occurrence and provide recommendations based on this review (e.g., that the study may continue or they may recommend modifications, including additional tolerability and efficacy measures). Every six months the DSMB will formally review all adverse events as well as all efficacy and tolerability data. Dr. Romo-Nava will be responsible for providing updated efficacy and tolerability data to the DSMB every six months and the person with the blinded information will provide information on treatment group assignment without breaking the blind. The DSMB will assess the risks and benefits of study participation to all subjects and based on this assessment the DSMB will provide a written report of their analyses and recommendation as to whether the study should continue, modifications to the study are needed or if the study should be terminated. Dr. Romo-Nava in conjunction with the DSMB, will be responsible for making certain that the DSMB files their report to the IRB and/or other authorities as required. The DSMB will also provide the investigator with a summary of their report that will include their recommendations.

Adverse events will be monitored during the study by the clinical research team, which includes Psychiatrists and a Neurologist and collectively have extensive experience conducting clinical investigation of mood disorders and in the case of Dr. Awosika, the use of transcutaneous spinal direct current stimulation for neurological rehabilitation. They also will be responsible for evaluating and documenting all adverse events during study visits or more frequently as necessary. Additionally, a study-related physician will be accessible by phone to patients 24 hours/day, 7 days/week during study participation. Dr. Romo-Nava and designated clinical researchers will be responsible for reviewing all laboratory and safety measures from all subjects following each visit. An adverse event (AE) is any unexpected medical occurrence in a patient or clinical investigation subject who is administered a product and which does not necessarily have a causal relationship with the treatment. This includes any clinical or laboratory change that occurs at any time following consent that does not typically occur in that subject and is considered clinically significant. The frequency and severity of all observed or volunteered AEs regardless of treatment group or suspected causal relationship to the study treatment will be recorded throughout the study. Dr. Romo-Nava and designated clinicians will also be responsible for determining causal relationships between the study treatment and all AEs. Withdrawal from the study as a result of an AE or because of therapeutic measures taken to treat an AE will be at the discretion of the PI. If a subject withdraws or is withdrawn from the study for any reason, a study physician will monitor subjects with any ongoing AE until the AE is resolved or determined to be stable. All AEs (including those present during screening) will be reported. However, for analytics purposes, only post-baseline (randomization) AEs (or AEs that are present at visit 1/ baseline but have increased in severity or frequency post-baseline) will be considered for calculating treatment group differences in AEs. All AEs will be reported to the study DSMB, and the IRB at the time of progress reports.

A serious adverse event (SAE) is any adverse experience occurring during study participation that results in any of the following outcomes: death; a life threatening adverse drug experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability/incapacity; or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse events when, based on appropriate medical judgment of the study physician, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes in this definition. The judgment of whether a particular AE meets the above criteria for an SAE for the proposed study will be determined by the PI, in conjunction with the proposed Data Safety Monitoring Board (DSMB). It will also be the PIs responsibility to manage all SAEs and to make referrals for appropriate care, as necessary. All SAEs will be reported to the University of Cincinnati Institutional Review Board and the study DSMB within 48 hours of their discovery. The study blind will be broken at any point throughout the study as needed to protect the safety of a subject. A person with the blinded information will be available 24 hours/day, 7 days/week if it is necessary to break the blind in an emergency situation. All subject information will be de-identified when reporting serious adverse events. All AEs and SAEs will be double entered into two separate databases (and checked for accuracy) that are de-identified and password protected to ensure confidentiality. Dr. Romo-Nava and the study team will ensure that all patients have appropriate follow-up care

options after their study participation, as previously described.

K. DATA AND SAMPLE STORAGE AND CONFIDENTIALITY.

All subject information/binders will be kept in locked file cabinets behind locked doors in the locked research suite. Subject binders will contain identifiable information. A master file/key with subject identifiers (typically initials and date of birth) will be kept in a locked password protected database to which only relevant study staff will have access. Subject information will be placed in a password-protected computer database, and will be available only to the principal investigators and research team members who are directly involved in entering and analyzing the data. The master file/key will exist until all study related analyses and publications are completed. Every effort will be made to maintain the confidentiality of study records. Agents of the University of Cincinnati Medical Center Institutional Review Board and the Lindner Center of Hope may be allowed to inspect records related to this study. The data obtained from the study may be published; however, participants will not be identifiable in such publications. Participant identity will remain confidential unless disclosure is required by law. The records of this research study will be kept confidential and will not be given to anyone who is not helping conduct this study unless specifically requested and waived by the participant. To further ensure confidentiality, study records will be kept in locked file cabinets and/or in computers and tablets with passwords, all in locked rooms here at the Lindner Center of Hope. Additionally, participant identification is coded with letters and numbers to de-identify individuals. As required, this study will be in full compliance of HIPAA.

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