Electroconvulsive Therapy for Traumatic Memories: A Randomized Controlled Clinical Trial

PROTOCOL

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Summary

Specific Aim: The goal of this trial is to test whether electroconvulsive therapy (ECT) can reduce the intensity and distress caused by traumatic memories, when administered immediately after reactivation of those memories.

Background: Traumatic events contribute to the genesis of disorders such as post-traumatic stress disorder (PTSD) and depression, and memories of the event can cause ongoing distress. Short-term episodic memories are encoded by the hippocampus and gradually become consolidated through reciprocal connections with the cortex, resulting in long-term memories being stored in a distributed network throughout the cerebral cortex. There are no effective treatments currently for specifically targeting traumatic memories and reducing the distress they cause.

ECT is the most effective treatment for improving mood in patients with depression and there is new evidence emerging that suggests ECT can also improve PTSD symptoms independently of co-morbid depression. In addition, the main side-effect of ECT is memory loss, specifically for autobiographical details surrounding the course of ECT, but not typically affecting long-term episodic memory, nor procedural memories. Memories stored in the hippocampus are vulnerable to disruption by ECT because they rely on synaptic changes that are mediated by relatively unstable modifications in AMPA receptor and metabotropic glutamate receptor density. We propose to exploit this feature of ECT, which normally is considered an undesirable side-effect of treatment, in an attempt to selectively reduce traumatic memories and the distress associated with them.

Our hypothesis is in part based on a recent study that demonstrated that ECT can significantly disrupt the recall of an emotionally aversive story if it was re-activated immediately before each ECT treatment session. (The difference between that study and our proposal is that the stories in that study were created by the experimenters and were not part of the subjects' real life experience.) Moreover, there is good evidence in the literature that the physiological responses to the recall of a traumatic memory can be halted if intervention occurs immediately after the trauma itself: the administration of propranolol in one trial given during traumatic memory reactivation was sufficient to reduce autonomic responses to the traumatic memory one week later. Therefore, we want to test if reactivation of traumatic memories coupled with ECT treatment can similarly reduce the effect of those memories in PTSD patients.

Methods: We propose to recruit 40 CAMH patients referred for ECT, who also have traumatic memories that are causing distress. These patients will be asked to write two narratives, one of the traumatic memory, and the other of a trivial, non-traumatic remote event. Patients will then be asked to listen to an audio recording of either the traumatic memory or the neutral memory (control group) immediately before their ECT sessions. The severity of the traumatic memory-related symptoms will be assessed before and after the course of ECT using the Modified PTSD Symptom Scale (MPSS-SR) and the Clinician Administered PTSD Scale for DSM-5 (CAPS-5). Data will be analyzed by comparing the change in overall MPSS-SR scores and CAPS-5 scores pre- and post-ECT between the experimental and control groups.

Expected outcome: We predict that patients with traumatic memories who hear a narrative of their traumatic memory immediately before ECT will experience a significant reduction in distressing symptoms related to the traumatic memory, compared to patients who hear a neutral, non-traumatic memory.

Significance: This study will demonstrate, for the first time, the efficacy of a treatment specifically targeted at reducing the intensity of traumatic memories, and the distress they cause.

ECT for Traumatic Memories: A Randomized Controlled Clinical Trial

Hypothesis

This proposal will test the hypothesis that the reconsolidation of traumatic memories can be disrupted by ECT, when administered immediately after re-activation of the traumatic memory through listening to a recorded description of the subject's own trauma.

Specific Aim

The specific aim of this proposal is to perform a randomized controlled clinical trial with patients receiving ECT who have distressing traumatic memories, including patients with or without psychiatric comorbidities. The specific intervention to be tested is reactivation of the traumatic memory 15 minutes before each ECT treatment, compared with control subjects who will instead reactivate a neutral, non-traumatic memory.

Background

Epidemiology of PTSD

PTSD was originally described in soldiers exposed to horrific battlefield events, but the conception of psychological trauma has since been expanded to include any life or limb-threatening events in either the military or civilian population. PTSD symptoms include flashbacks and nightmares of the traumatic event, avoidance of reminders of the trauma, negative mood or thoughts including blaming oneself for the trauma, withdrawal from previous interests and feeling detached. Hyperarousal is also common, and manifests as irritability, poor concentration, insomnia, hypervigilance and being easily startled (American Psychiatric Association, 2013).

PTSD affects up to 18% of military combat veterans (Lawson, 2014), with about the same percentage (19%) of victims of physical assault similarly affected (Johansen et al., 2013). Approximately 2% of US military personnel report having PTSD symptoms (Smith et al., 2009). There is considerable overlap in symptoms between patients with Major Depressive Disorder (or simply depression) and PTSD (Gros et al., 2012). The majority of PTSD patients have a co-morbid psychiatric diagnosis, most commonly depression (Brady et al., 2000). Patients who engage in deliberate self-harm are also likely to have had a history of trauma and current PTSD and depression symptoms (Jaquier et al., 2013).

Existing treatments for PTSD

The most effective current treatment for PTSD is cognitive-behavioural psychotherapy, with an average effect size of 1 to 1.27 (Cohen's d on the Clinician-Administered PTSD Scale or CAPS) (Jonas et al., 2013), depending on the specific type of CBT. Exposure therapy is the most effective, and is aimed at desensitizing the patient to cues related to the traumatic even through gradual and repeated exposure. Cognitive restructuring consists of identifying and modifying cognitive distortions of the trauma, while stress inoculation training consists of teaching techniques to reduce anxiety and improve coping skills. In general, clinical trials assessing psychological treatments for PTSD have been of low quality (Bisson et al., 2013). However, there is some evidence to support that trauma-focused cognitive behavioural therapy, eye

movement desensitisation and re-processing, and non-trauma-focused cognitive behavioural therapy can be helpful for PTSD symptoms (Bisson et al., 2013).

Medications are generally less effective than CBT, with an effect size about half that of CBT (Jonas et al., 2013). There are only two medications currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of PTSD: sertraline and paroxetine, both of which are selective serotonin re-uptake inhibitor antidepressants. A recent Cochrane Database systematic review evaluated combined therapy and medication treatment for PTSD. "There is not enough evidence available to support or refute the effectiveness of combined psychological therapy and pharmacotherapy compared to either of these interventions alone. Further large randomised controlled trials are urgently required" (Hetrick et al., 2010). All the trials surveyed consisted of combined SSRI and cognitive behavioural or exposure-based interventions.

A significant proportion of patients with PTSD have spontaneous remission of symptoms, depending on a number of factors, such as the nature of the trauma and the time interval since the trauma (Morina et al., 2014). Despite the treatments reviewed above, overall functioning and outcomes for patients with PTSD remains poor (Murdoch et al., 2011). The presence of PTSD significantly reduces the rate at which patients suffering physical traumatic injury can return to work (Zatzick et al., 2008). Stable remission of chronic PTSD is rare (Shalev, 2009), and thus there is a need for additional and better treatments for PTSD symptoms.

Emerging new treatments for PTSD

Several experimental treatments for PTSD that are relevant to this proposal include prazosin, D-cycloserine and propranolol. Prazosin reduced the psychological distress induced by a trauma-related word list when given during the day in addition to a bedtime dose to suppress trauma-related nightmares (Taylor et al., 2006). D-cylcoserine activates the glycine binding site at the NMDA receptor that enhances channel opening in addition to glutamate. D-cycloserine can enhance extinction of fear memories in rodents. It is also able to amplify the effects of exposure therapy in patients with phobia (Ressler et al., 2004), and thus has promise as an adjunctive treatment for PTSD (Choi et al., 2010). Propanolol has been shown to reduce both consolidation and reconsolidation of emotional memories such as words with negative valence, stories and cued fear responses (Lonergan et al., 2013). There is good evidence that propranolol can reduce the physiological responses to the recall of a traumatic memory if administered immediately after the trauma itself. There is one clinical trial with propranolol given during traumatic memory reconsolidation (Brunet et al., 2008). In that small study of 9 propanolol and 10 control subjects, one reactivation session with a traumatic script, followed by a single dose of propanolol was sufficient to reduce autonomic responses to the traumatic memory one week later. However, the data supporting these novel pharmacological treatments remains preliminary, and there are no definitive clinical trial results available. It is likely that no single new treatment will be effective in every patient. It would be prudent to explore a number of different therapeutic approaches to optimize overall outcome for patients with PTSD symptoms.

Memory consolidation, reconsolidation and ECT

Short-term episodic memories are stored first in the hippocampus, which makes reciprocal connections throughout the cerebral cortex. Over time, memories that are retained become increasingly dependent on these cortical areas for maintenance (Frankland and Bontempi, 2005). This process is referred to as memory consolidation, which in addition to changing the physical location of the memory, also involves different cellular and molecular

mechanisms of memory storage than short-term memories (McGaugh, 2000). Protein synthesis and the modification of synaptic connections is required for establishing long-term memories (Kandel, 2001), while short-term memories are stored by more rapid modifications of AMPA receptor expression and glutamate release (Kauer and Malenka, 2007). Protein synthesis inhibitors and ECT can both disrupt consolidation of memories (Frankland et al., 2004; Fraser et al., 2008). When a memory is retrieved in the present, it again becomes liable to disruption by the same interventions that impair consolidation (Nader et al., 2000; Kroes et al., 2014). Thus, re-activated memories undergo a reconsolidation, or updating consolidation when new information modifies the original memory (Rodriguez-Ortiz and Bermúdez-Rattoni, 2007).

The encoding of traumatic memories can be modeled in rodents using fear conditioning paradigms. These procedures pair the delivery of an unconditioned fear-inducing stimulus like a mild foot shock, with a conditioned stimulus such as the context of a particular cage, or a discrete stimulus such as an auditory tone or flashing light. Using this kind of behavioural paradigm, it is now known that specific neurons in the amygdala encode specific fear-context associations in a CREB (cAMP response element-binding protein)-dependent manner (Han et al., 2007), and that removal of these neurons is sufficient to permanently erase the fear memory (Han et al., 2009). Thus, if the neurons encoding a specific memory trace can be targeted for a memory disrupting intervention, it is possible in principle to selectively reduce or remove that particular memory. The reconsolidation of an aversive memory was successfully impaired using localized intracranial electrical stimulation in the rat (Stehberg et al., 2009). The methods used experimentally in animals are of course not suitable for human clinical use, but ECT is an existing clinical treatment that has powerful effects on memory.

ECT is the most effective treatment for depression, and the evidence for this comes from many well-designed, high-quality randomized clinical trials (Eranti and McLoughlin, 2003; UK ECT Review Group, 2003). There is a case report (Helsley et al., 1999), a retrospective chart review (Watts, 2007) and an open clinical trial (Margoob et al., 2010) suggesting that ECT can improve PTSD symptoms independently of co-morbid depression. However, none of those studies used a memory re-activation strategy, nor were they prospective randomized clinical trials. The main side-effect of ECT is memory loss, specifically for autobiographical details surrounding the course of ECT, but not typically affecting long-term episodic memory, nor procedural memories (Fink and Taylor, 2007). Here we propose to exploit this feature of ECT, which normally is considered an undesirable side-effect of treatment, in an attempt to selectively reduce traumatic memories and the distress associated with them. A recent paper demonstrated that ECT can significantly disrupt the recall of an emotionally aversive story only if it was re-activated immediately before each ECT treatment (Kroes et al., 2014). The control comparison was a similar, but not re-activated memory of a different story. Both stories were created by the experimenters and were not part of the subjects' real life experience, which is the main difference between that study and this current proposal.

Standard care and treatment milieu for study patients

Subjects for this study will be recruited from the Women's Inpatient Unit on the 9th floor of the Centre for Addiction and Mental Health, College Street site (9-WIU). 9-WIU is a short-stay 18-bed inpatient unit for women with severe mental illness or mood and anxiety disorders who may have experienced trauma (childhood sexual, physical and emotional abuse and/or sexual or physical assault in adulthood) and /or addiction. Individualized treatment includes

assessment, diagnostic clarification, stabilization, focused treatment interventions and facilitation of community linkages.

9-WIU provides treatment based on the Sanctuary model of care, in which all staff are trained in trauma informed care and use dialectic behavioral therapy principles. 9-WIU is rated as a stage 1 trauma treatment program. Most admissions come from the emergency department and the prime goal of the admission is to have patients attain stability. Developing the patient's narrative is part of the work that is done in the inpatient 9-WIU setting. As a starting point, patients are asked to just list their traumatic memories and experiences. The most bothersome memory is then suggested to be described in some detail. Patients are assessed for safety throughout this process, are supported and validated. Their thoughts and feelings around the trauma are encouraged to be expressed. There is evidence that writing about emotional or traumatic experiences can be helpful in a number of mental health domains (Pennebaker, 1997).

Since the patients are already reflecting and thinking about their traumatic experience(s) as part of their treatment, involvement in this study should not generate additional stress. However, trained staff from 9-WIU will be available at all times, in case the process of writing a detailed narrative of the traumatic experience(s) or listening to the recording is found to be distressing. Having a staff member from 9-WIU present during the process will help support the patients, as well as assess their safety. If at any time the staff from 9-WIU believes a patient is too distressed or unsafe to continue in the study, the patient will be removed from the study.

Trial design

We propose a randomized controlled trial in which 40 patients referred for ECT who also have distressing traumatic memories will be invited to participate. Subjects meeting the inclusion criteria below will undergo a structured evaluation of their diagnosis using the MINI, and quantification of their trauma-related symptoms using the scales listed below, both before and after their course of ECT, will be done. To re-activate the traumatic experience(s), we will be using script-driven imagery (SDI), a method previously used to study or treat PTSD (Pitman et al., 1987; Rauch et al., 1996; Isserles et al., 2013). Each subject will be asked to complete a script preparation form, which includes a section for describing the traumatic experience (or the most traumatic experience) as well as a list of physical symptoms that may have accompanied the experience. Subjects will then complete this same form again, however this time describing a neutral experience.

Each patient's script will be prepared according to a published procedure (Pitman et al., 1987). The script will be approximately 30 seconds in length, written in second person and present tense, and will incorporate 5 of the physical symptoms selected by the patient. A CAMH clinician from 9-WIU who is not directly involved in the study will record the scripts in a neutral voice. The two recordings will be randomly labeled as "A" or "B" by the individual who recorded the scripts. Subjects will then be randomized to either group A or B, and will then be asked to listen to the recording immediately before each ECT treatment session. The study personnel are thus blind to the intervention group (re-activation of the traumatic memory vs. re-activation of a non-traumatic memory). The subjects themselves will not be blind to the intervention being investigated since they must actively listen to the script describing the traumatic or non-traumatic event.

Traumatic memory-related symptoms will be assessed with the Modified PTSD Symptom Scale (MPSS-SR) and the Clinician Administered PTSD Scale for DSM-5 (CAPS-5). The MPSS-SR is a 17-item self-report measure that assesses the DSM-III-R symptoms of PTSD,

and it is a modification of the PTSD Symptom Scale (PSS). The MPSS-SR records symptoms that are not specific to a particular traumatic event and includes severity ratings in addition to the PSS frequency ratings for each item. This is useful for our study, as subjects may have single or multiple event traumas. The MPSS-SR can be used to assess response to treatment in its total score or its sub-domain scores (re-experiencing; avoidance-numbing and hyperarousal). It can also be used to make a preliminary determination of the diagnosis of PTSD using dichotomous scoring. We have chosen a MPSS-SR re-experiencing score (items 1-4, 17) cut-off score of 20 since 23 on this subset of items is the approximate threshold for a PTSD diagnosis. We are attempting to select patients who have definite re-experiencing symptoms of trauma, but who may not necessarily meet the formal criteria for PTSD.

The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) is a 30-item semi-structured interview that is used to make a current (past month) or lifetime diagnosis of posttraumatic stress disorder (PTSD) and to provide a continuous index of PTSD severity. It also can be used to assess PTSD symptoms over the past week. In addition to assessing the 20 DSM-5 PTSD symptoms, questions target the onset and duration of symptoms, subjective distress, and impact of symptoms on social and occupational functioning, improvement in symptoms since a previous CAPS administration, overall response validity, and features for the dissociative subtype (depersonalization and derealization). Administration requires identification of an index traumatic event to serve as the basis for symptom inquiry. The Life Events Checklist for DSM-5 (LEC-5, see Trauma Adversity and Exposure) is recommended prior to the Criterion A inquiry included in the CAPS-5. Standardized questions and probes are provided for each symptom.

Subjects

Patients with depression and traumatic memory symptoms who have been approved for ECT treatment at CAMH will be screened for eligibility to participate in this study. Patients must be adults (aged 18+), be capable of informed consent, and be approved for ECT treatment according to standard clinic procedures, through a formal consultation with an ECT psychiatrist and an anesthesiologist on the ECT service. Other psychiatric diagnoses are not part of the inclusion criteria, but will be assessed and recorded.

Inclusion criteria:
1) Patient referred and accepted for ECT treatment at CAMH
2) Presence of traumatic memories
3) Able to write about their traumatic experience(s)
4) Capable of informed consent to participate in this study
5) Age 18 or greater
6) MPSS-SR re-experiencing score (items 1-4, 17) ≥ 20

Exclusion criteria:
1) History of neurological or developmental disorder, including seizures
2) ECT treatment already started

Recruitment

After approval to proceed with ECT has been granted, the ECT or 9-WIU staff will identify potentially eligible subjects. During the consultation with the ECT psychiatrist, it is standard practice to mention studies that are currently being conducted in our clinic, including

magnetic seizure therapy (MST) or transcranial magnetic stimulation (TMS) studies. Similarly, the consulting psychiatrist may describe this ECT-PTSD study to the patient and ask if they are interested in participating. If the patient expresses interest, the ECT clinic or 9-WIU staff will then notify the graduate student assigned to this study, who will approach the patients to ask whether they might be interested in participating.

Study visits and schedule

Visit 1: Patients will be screened for eligibility and consent obtained. If eligible and enrolled, the patient will be asked to complete the MINI, the Modified PTSD Symptom Scale (MPSS-SR) and the Clinician Administered PTSD Scale for DSM-5 (CAPS-5). Subjects will also be asked to write two script preparation forms, with instructions to write an approximately one-page recounting of:

(1) the most problematic and prominent traumatic memory on one piece of paper, and

(2) a neutral, non-traumatic memory of no emotional significance on the other paper.

Patients will also be asked to identify physical symptoms associated with both of the narratives described. Trained staff from 9-WIU will be available at all times, in case the process of writing a detailed narrative of the traumatic experience(s) is found to be distressing. The non-traumatic memory will consist of a description of a typical and unremarkable sequence of events, such as the patient's morning routine (e.g. a narrative of making breakfast and personal hygiene procedures). A study investigator will then transform the subject's written descriptions into about 125 word long "exposure scripts" in the second person, present tense. These exposure scripts will be then given to a CAMH clinician from 9-WIU not directly involved in the study, who will record the scripts in a neutral tone. The same CAMH clinician will narrate all the recordings in order to standardize the scripts in tone and length. All recordings will be approximately 30 seconds in length and the traumatic script will include five of the physical symptoms described by the patient. The script recording is preceded with short instructions for the subject to concentrate on the script and to imagine the described experience for additional 30 seconds right after the script until a short beep sounds. Each recording will be stored as an MP3 file and labelled randomly as "A" or "B" and with the patient's study identifier number. This process will help to maintain anonymity for the subjects and also blind the research team to the content of the recordings. No other subject identifiers will be stored on the MP3 player.

Each patient will then be randomized to listen to either recording A or B for the duration of the study.

ECT session visits: Approximately 15 minutes before each ECT treatment session, subjects will be asked to sit briefly in an assessment room in the Brain Stimulation Clinic with a member of the research or clinical team. The researcher will go over the protocol, and answer any questions the subject may have. When the subject enters the treatment room, they will be handed an MP3 player with either recording A or B, depending on the intervention group. The patient will have several minutes to listen to the recording while the standard pre-ECT procedures are conducted. Subjects will have the option to use their own headphones, plugged into the study MP3 player, or will be provided with headphones. Trained staff from 9-WIU will be available during the process of script driven imagery. ECT will then proceed as usual.

Visit 2: Subjects will complete the MPSS-SR and the CAPS-5 again, immediately after the last ECT treatment session. This should take about 45-60 minutes.

Visit 3, three-month follow-up: Subjects are asked to complete the MPSS-SR and the CAPS-5 again. This should take about 45-60 minutes.

The study will not interfere with standard of care in any way. Patients will come to the ECT sessions as they normally would and after listening to the recording, ECT will proceed as usual. All staff will be blind to the intervention group, including the physician overseeing the patient's ECT treatment.

Data analysis plan

The change in MPSS-SR scores and CAPS-5 scores between subjects reactivating the traumatic memory and subjects reactivating the non-traumatic memory will be compared with a repeated measures ANOVA, after testing for normal distribution of the data using the Shapiro-Wilk test. Based on the reported effects of ECT on memory reconsolidation (Kroes et al., 2014), and the magnitude of other treatment effects on the psychological distress associated with traumatic memories (Taylor et al., 2006), we estimate that 15 patients in each group should be sufficient to detect significant effects of memory reactivation before ECT. Kroes et al. found significant effects of ECT on memory reconsolidation with 13 subjects per group. Thus, we aim to recruit a total of 40 patients for this study (20 per group), with the expectation that at least 30 will complete the entire protocol. ECT variables might affect the outcomes, and we will collect data on the number and type of ECT treatments, the frequency of ECT visits, seizure duration and anesthetic medication doses, to be included as covariates in our statistical analyses.

Significance and Impact

If successful, this study has the potential to contribute very significantly to the understanding of PTSD, and to advance the treatment of this important psychiatric disorder. The traumatic memory reactivation procedure is a very feasible and practical intervention that could easily and quickly be translated into clinical practice. The effect of memory reactivation in combination with ECT would also advance our general understanding of traumatic memory and memory reconsolidation. This knowledge will help in the exploration of other PTSD treatments aimed at disrupting traumatic memories through exploiting the reconsolidation mechanism.

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