ORGANIZATION OF DETAILED PROTOCOL

Title: Boston-Harvard Burn Injury Model System: Cortical modulation with transcranial direct current stimulation (tDCS) for neuropathic symptoms following burn injury.
Protocol #: 2012-p-001996
Date: 03/21/2016

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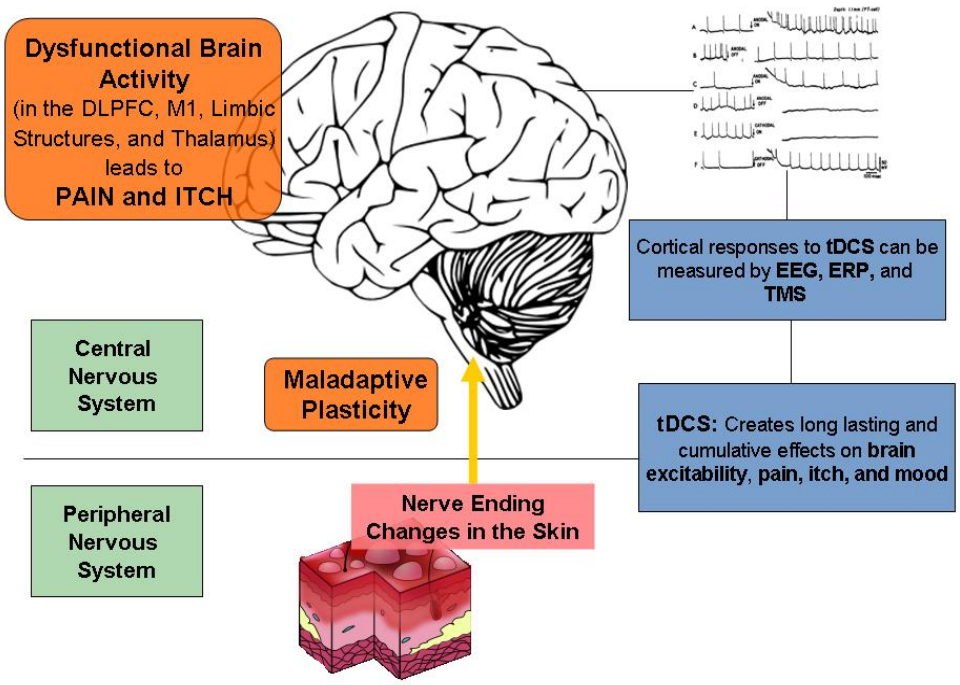
Dysfunction of Neural Pathways in Burn



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II. SPECIFIC AIMS

The overall goal for this project is to develop a novel treatment using transcranial direct current stimulation (tDCS) for patients with neuropathic burn symptoms such as pain or itching. Because the interventions to date for this group of patients (mainly drugs) have been marked by limited clinical effectiveness [14], the results of this study will represent an initial, significant step toward providing a new therapeutic alternative to this group of patients. Finally we will also collect neurophysiological data to understand further the mechanistic effects of this novel intervention and compare with the use of tDCS for other chronic pain syndromes.

The following aims will be explored in this study:

Aim 1 - To assess the effects of tDCS treatment on neuropathic symptoms: pain or itching – following burn injury. We will determine the magnitude of pain reduction with the modified Brief Pain Inventory (BPI) and itch severity/activity with the Visual Analog Scale (VAS) and 5-D Scales in active tDCS compared with sham tDCS. *Our first hypothesis is that active tDCS will be associated with a larger pain or itching reduction assessed by BPI and Itch VAS/5-D.*

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IV. SUBJECT SELECTION

We will select 60 subjects that have burn injury and meet the following criteria:

Inclusion Criteria:

1. Providing informed consent to participate in the study
2. Age 18 or older
3. Burn injury with pain and/or itch that is moderate to severe (at least 4 on the visual analogue scale during the previous 3 weeks)
4. Burn injury occurred at least 3 weeks prior to enrollment. Patient must be discharged from acute inpatient care. (Patient can be enrolled in either inpatient rehabilitation and/or outpatient care)

Exclusion Criteria:

1. Subjects with burns in scalp in the area of electrode placement (i.e. within 4 cm of the DLPFC and the reference site) as the electrode may cause irritation to the injuries
2. Psychiatric disorders that have led to hospitalization within the past 6 months or signs of suicidality
3. Learning disorders that may affect the patient's ability to complete assessments.
4. Unstable conditions preventing travel to the study site

5. Current use of any anti-epileptic medications or dopaminergic medications known to reduce or inhibit the benefits of tDCS treatment: carbamazepine, oxcarbazepine, phenytoin
6. Contraindications to tDCS including implanted metal plates in the head or implanted brain medical devices
7. Pregnancy
8. History of other neurological conditions associated with structural anatomical changes (i.e. stroke, brain injury, Parkinson's)

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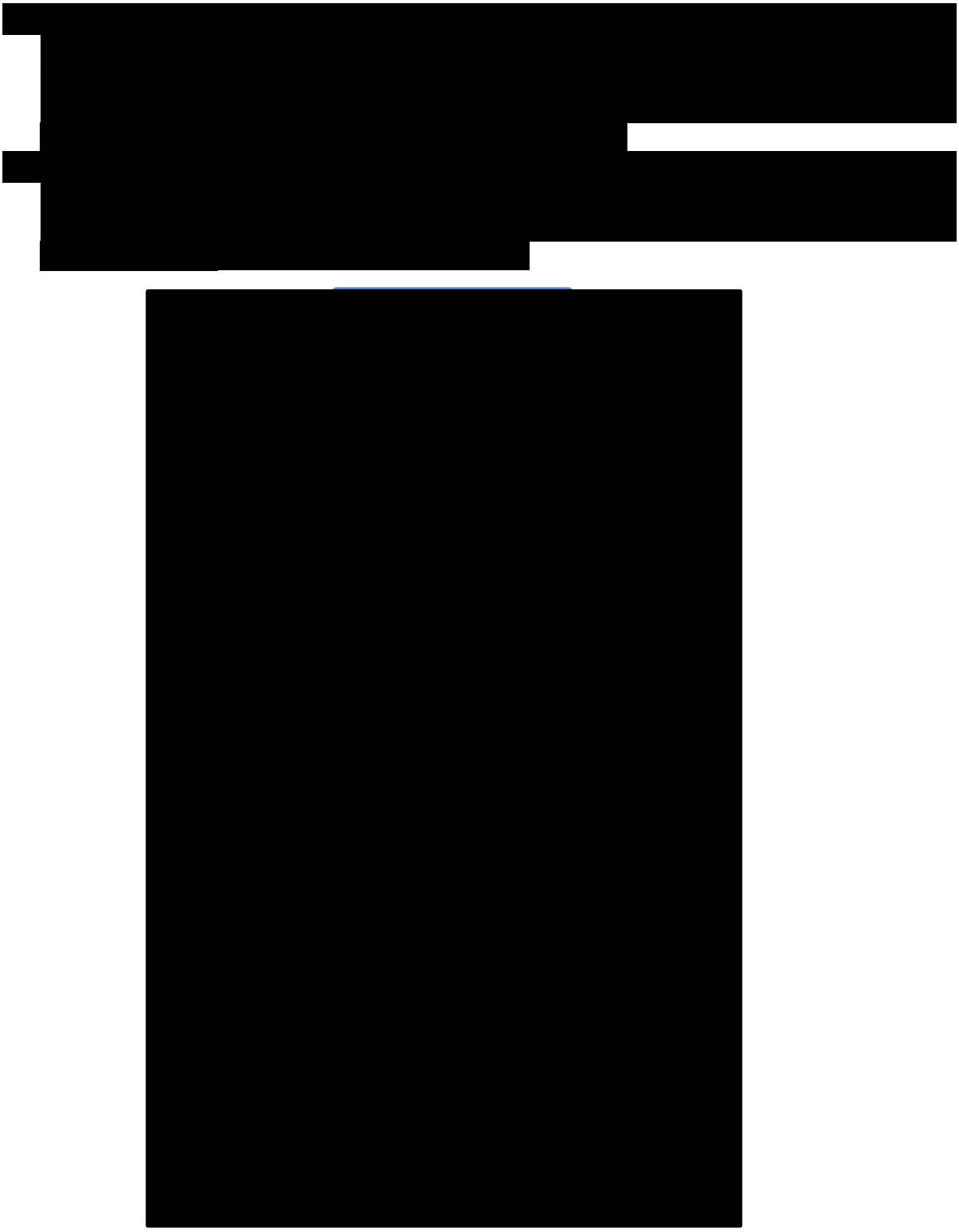

VI. STUDY PROCEDURES

We will select sixty participants that have burn injury and meet the inclusion criteria proposed. Study visits will take place at either Spaulding Rehabilitation Hospital (SRH) or Spaulding Rehabilitation Network Research Institute (SRN-RI). Subjects will be thoroughly informed of their study visit location prior to enrollment.

Please note: for subjects who enroll as inpatient into the study, we will coordinate with the appropriate care outlets to ensure that the procedures of the study will not interfere with their standard of care. This includes, but is not limited to: physicians, therapists and nurses working with the patient. We will schedule inpatients as their clinical schedule allows – preferably after 3pm – unless the patient specifies otherwise. We will also attempt to target patients toward the end of their rehab stay when they are less medically complicated (ex. fewer changes in medications/treatments etc.) and may be more independent in their travel. When possible/feasible, we will also complete study visits in the patients' room in order to limit time off of the floor.

Subjects will receive either (i) active tDCS; or (ii) sham tDCS in a randomized double blind design. Randomization assignment will be kept in a locked cabinet accessible only to the unblinded study investigator.

The study will occur in three parts, where the subject consents to Part I (Visit 1), then if they choose to continue, they may consent to Part II (Visits 2-14). After completion of Part II, they may then choose to consent to Part III (Visits 15-23).

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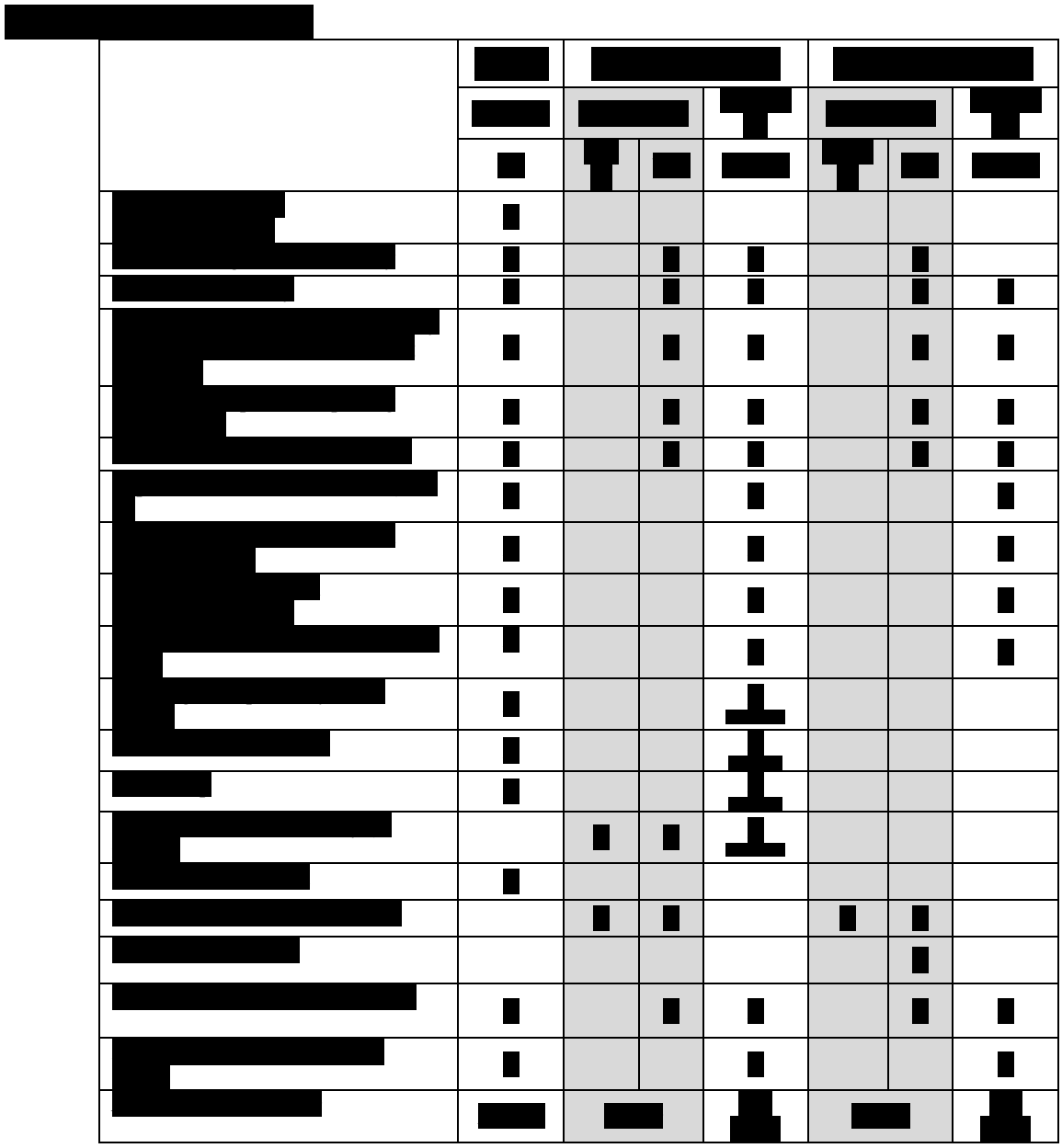

Detailed Protocol 13

DESCRIPTION OF ASSESSMENTS

Demographic Assessment: We will record the following baseline characteristics: age, sex, race/ethnicity and level of education.

VAS for Anxiety: This is a self-evaluation scale that ranges from 0 to 10, where 0 means no anxiety and 10 means the worst anxiety ever. This scale is used extensively in our tDCS studies [46, 54-56, 60, 62].

Modified Brief Pain Inventory (BPI) – main outcome: The BPI is a short self-assessment questionnaire that provides information on various dimensions of pain including how pain developed, the types of pain a patient experiences, and time of day pain is experienced, as well as current ways of alleviating pain [83]. The BPI also consists of the VAS Pain scale, a simple 10-point scale (0 = ''no pain'', 10 = ''pain as bad as you can imagine'') measuring a patients' worst pain and least pain, on average and at present time. The Brief Pain Inventory provides information on the intensity of pain (the sensory dimension) as well as the degree to which pain interferes with function (the reactive dimension). According to several previous studies on pain in spinal cord injury, the BPI is an effective measure, as shown by both our group [54] and other studies [84]

Itching Severity: We will measure severity of itching using a VAS for itching severity. This is a 0 to 10 scale, where 0 indicates no intensity and a 10 indicates unbearable intensity of itching. This scale has been previously used in a study investigating treatment of refractory itching in burn patients. We will also have subjects keep a record of itching/pain severity using this scale in a diary through visit 12.

Itching Activity: We will also measure scratching activity using VAS for scratching activity. This is a 0 to 10 scale, where 0 indicates no activity of scratching and a 10 indicates frequent scratching activity. This scale has been previously used in a study investigating treatment of refractory itching in burn patients. We will also have subjects keep a record of itching/pain activity using this scale in a diary through visit 12.

5-D Itch scale: We will use this scale to measure five dimensions of itch: degree, duration, disability, and distribution. It is a valid and reliable for measuring itch and changes in itch over time

Beck Depression Inventory (BDI): The Beck Depression Inventory (BDI) is a 21-item test presented in multiple-choice format that measures the presence of and the degree of depression in adults [85]. If an enrolled subject gives a response of a of 1, 2 or 3 on question 9 on the BDI, the subject will be withdrawn from the study and the medical coverage will be contacted immediately by research staff to provide further evaluation and action to protect the subject (i.e. if the subject needs to be escorted or referred to the MGH ED Acute Psychiatry Service).

Impact of Event Scale Revised (IES-R): This 22-item scale is designed to measure severity of PTS symptoms associated with a traumatic event. These symptoms correspond to the symptoms

contained within the DSM-IV. Subjects are asked to rate their level of distress associated with the event on a 0-4 scale (0 means not at all distressed, 4 means extremely distressed). This scale has been extensively validated[86]

Veterans RAND 36 Item Health Survey (VR-36): The VR-36 was developed by our collaborators [87]. This survey was developed from the Veterans Health Study and includes both physical and psychological domains as a measure of overall quality of life. There are eight domains total including: bodily pain, role limitations due to physical problems, physical functioning, general health perception, vitality, social functioning, and role limitations due to mental health issues. This measure is valid and reliable[87].

Community Integration Questionnaire (CIQ): This instrument measures home integration competency, social integration, and productive activity[88]. It assesses levels of independence and interdependence. It includes questions about leisure activities, social interactions, travel/mobility, and daily activities; it contains a rating scale of how easily these items are accomplished (i.e. often/never, done alone/done with someone else, full time/not applicable). This assessment has been validated for use[88].

Primary and Secondary Employment Status: As part of the vocational sub-aim of this study, we will assess the employment status, and in particular the intention to seek employment, of each subject. Codes include: unemployed, unemployed but searching for work, part time or full time student, employed, or retired. These are the same employment rating scale codes used already in the model systems database.

Sleep Assessments: We will measure sleep outcomes using the Pittsburgh Sleep Quality Index, Insomnia Severity Scale, and VAS for sleep. We will also have the subjects keep a very short diary looking at sleep for the first 4 weeks of the study.

Medication Use Questionnaire and Diary: We will obtain a medication use history at study entry using a standardized questionnaire similar to that used in our prior tDCS studies, and update this information at each subsequent visit. We will also monitor patient medication throughout the course of the study using a subject Medication Diary. Participants will be required to record medications daily in a pain medication diary. Participants will be instructed to keep the pain medication diary throughout the baseline, treatment, and follow-up period. This diary will be maintained until completion of the study.

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VII. STATISTICAL ANALYSIS

As study outcomes will be measured at baseline and several timepoints up to 12 months (post-enrollment), continuous and categorical outcomes will be analyzed by methods of longitudinal analysis using generalized estimating equations with an unrestricted covariance matrix, to estimate model parameters and test hypotheses. Tests of equality of the change from baseline to 12 months in the two treatment groups will be based on the estimate of the time (12 months versus baseline) by treatment interaction. This will allow participants who are seen at some follow-up visits but not at 12 months to contribute to the analysis. Time to event variables such as time to return-to-work will be analyzed by proportional hazards regression and Kaplan Meier estimation of time to event distributions.

Midway through the study, a power analysis will be performed to reassess the sample size needed to successfully complete this project. In this analysis, we will only look at the variability parameters (variance) and compare it to the one estimated before the study. We will not look at the effect estimates and therefore do not anticipate Type I error increase. This power analysis will be performed by a staff member (Co-Investigator) not involved with the analysis and conduct of the study. All blinded staff members will remain blinded.

The primary endpoint for this study is pain intensity as measured by the BPI. The study will have three secondary endpoints: itch as measured by the VAS scale, depression as measured by BDI and neural activity changes measured by somatosensory ERPs. These secondary outcomes represent three domains in which tDCS are anticipated to be effective. The same analytic approach will be employed in the analysis of the primary and secondary outcomes. For the outcomes, exploratory univariate analysis comparing active vs. placebo tDCS will be conducted. If a significant treatment effect is detected, similar adjusted longitudinal regression analysis will be performed; however these analyses will be considered hypothesis generating a p values interpreted cautiously given the increased likelihood of a false positive result given the false positive problem.

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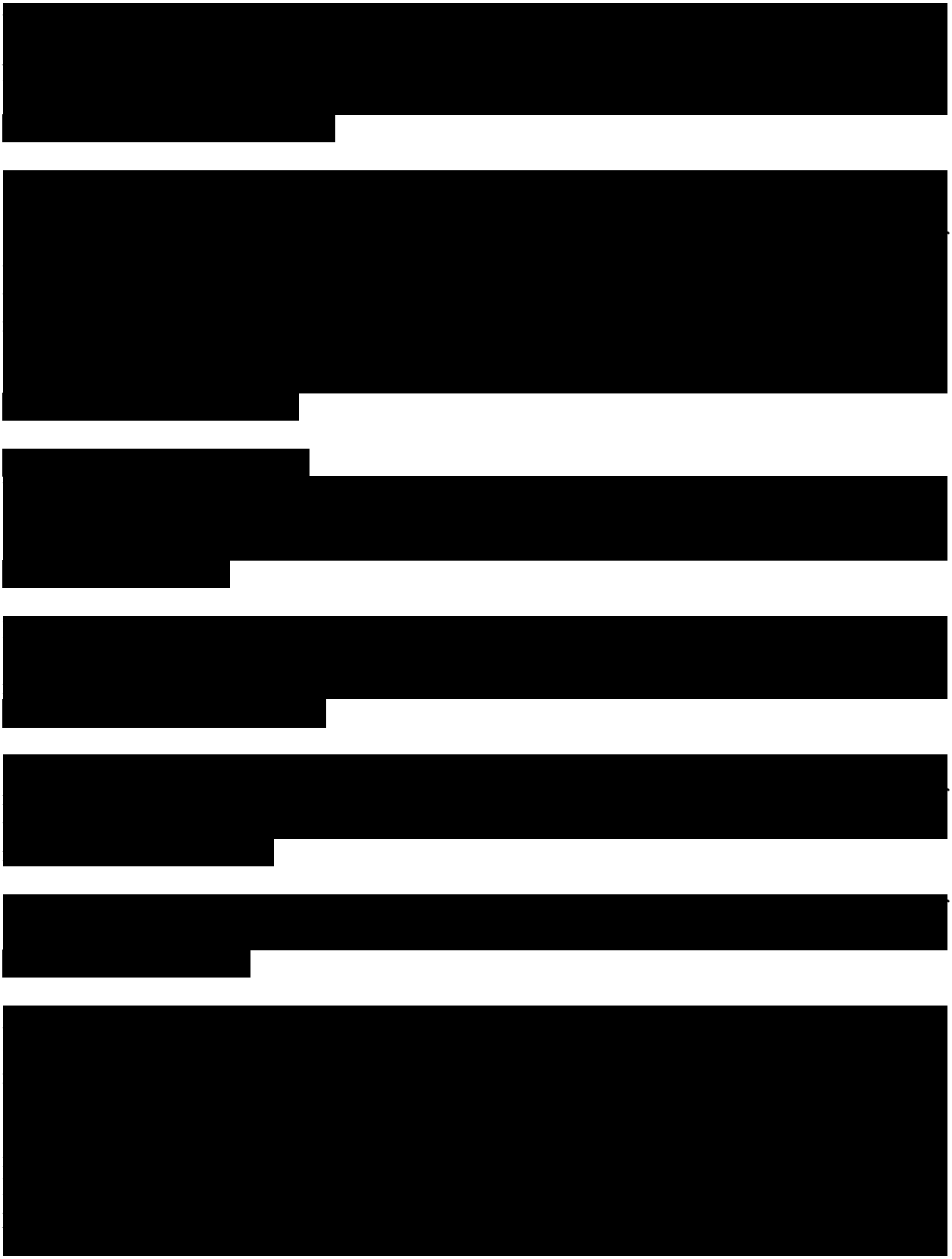

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