

ADDITIONAL INFORMATION

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OPEN

Is depression a disorder of electrical brain networks?

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Major depressive disorder (MDD) is one of the most prevalent and disabling neuropsychological disorders in the world, with 15% of adults expected to experience depression sometime in their lives. Current treatment options are largely ineffective, as only 50–70% of patients experience remission after multiple rounds of treatment [1]. Thus, there is a clear and immediate need for the development of novel therapeutics that prevent MDD. Nevertheless, this endeavor has been hampered by limited knowledge of the biology underlying the disorder.

A well-validated murine model of depression, chronic social defeat stress (CSDS) [2], can differentiate between mice that exhibit MDD-like behavior following stress exposure, termed “susceptible”, and those that do not, termed “resilient”. Our lab’s prior work exploring network dynamics linked to CSDS susceptibility found that susceptible mice exhibited greater prefrontal cortex (PFC)-dependent limbic synchrony [3]. Since susceptible and resilient mice experienced identical stress exposure but exhibited different network dynamics after CSDS, we hypothesized that differences in network dynamics exist prior to stress exposure and could serve as a biomarker for the vulnerable population of test mice (i.e., mice that will exhibit MDD-like behavior following future exposure to CSDS).

To test this hypothesis, multicircuit recordings during acute threat were collected from test mice before and after exposure to CSDS, and processed using discriminative cross-spectral factor analysis (dCSFA), a model of machine learning [4]. The dCSFA method was chosen for its interpretability (i.e., reliability to specific neural phenomena) and prediction (i.e., discrimination of behavioral variables). This approach identified four electrical network features, termed “electome factors”. These networks were validated using techniques previously demonstrated to increase vulnerability (e.g., early life stress, inflammation, and overexpression of the gene *Sdk1* in the ventral hippocampus). Only one of these electome factors,

Electome Factor 1 (EF1), was responsive to vulnerability manipulations and, consequently, validated as a network underlying vulnerability. Furthermore, techniques for treating susceptible mice after CSDS (e.g., ketamine administration and suppression of activity in PFC) did not have any significant effect on *EF1*, though these treatments suppressed other electomes associated with susceptibility. Activity in this network originates in the PFC and ventral striatum, relays through the amygdala and ventral tegmental area, and converges in the ventral hippocampus. Together, these results indicate that *EF1* is a biomarker of vulnerability and is distinct from MDD-like susceptibility.

Alternative techniques have identified networks indicative of individual vulnerability to social stress in rats [5]. Though vulnerability identification has not progressed to humans yet, recent functional magnetic resonance imaging studies in depressed patients have revealed distinct functional networks [6]. Furthermore, differences in functional connectivity successfully predict different subtypes of depression as well as responsiveness to treatment, suggesting that network-level analyses may provide an avenue for developing more successful treatments for depression.

Our findings demonstrate that network-level spatiotemporal dynamics can indicate previously obscured vulnerable individuals within heterogeneous populations. These results could support the development of novel therapeutic mechanisms targeted at preventing the emergence of MDD or encouraging resilience in vulnerable populations. Furthermore, they encourage exploration of electome networks that may signal other emotional states in health and disease.

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MDMA-assisted psychotherapy for posttraumatic stress disorder: A promising novel approach to treatment

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Posttraumatic stress disorder (PTSD) treatment guidelines have unequivocally designated psychotherapy as a first-line treatment, despite well-documented neurobiological alterations in this disorder [1]. Even with psychotherapy, PTSD often remains chronic and severe. There is urgency to discover novel compounds and new treatment strategies for PTSD.

One approach is the use of medication to leverage the effects of psychotherapy. A promising example is the use of 3,4-methylenedioxymethamphetamine (MDMA). MDMA was synthesized in 1912 by Merck and discovered in the early 1970s to enhance effects of psychotherapy. The subsequent classification of MDMA as a Schedule 1 controlled substance made its use in therapy illegal and created obstacles to clinical research, including assessment of safety.

Nonetheless, new research has emerged demonstrating the efficacy of MDMA as an enhancer of psychotherapy for PTSD. Recently, a pooled analysis was published from six small randomized, double-blind, controlled clinical trials of MDMA [2]. Patients were enrolled to manualized psychotherapy sessions in two or three 8 h sessions, spaced a month apart. They were given either active doses of MDMA ranging from 75 to 125 mg ($n = 72$) or placebo/control doses 0–40 mg ($n = 31$). Non-drug sessions lasting 90 min preceded the first MDMA exposure and three to four weekly sessions following the drug-facilitated session. Two clinicians facilitated an introspective process in which the patient revisited past experiences while under a mental state produced by MDMA that presumptively minimized fear, arousal, and avoidance of painful material. Under MDMA, patients experienced significantly greater

reductions in PTSD symptom scores than under placebo, with a treatment effect of 0.8. After two experimental sessions, double the participants in the active group (54.2%) did not meet PTSD diagnostic criteria than in the control group (22.6%). Based on these pooled results Food and Drug Administration (FDA) granted MDMA a breakthrough therapy designation for the treatment of PTSD. Yet, it will be important to continue to assess safety of MDMA, particularly when higher or multiple doses are used [3].

MDMA-assisted psychotherapy provides a novel approach for examining how the use of a medication that dramatically alters a cognitive state can facilitate a deeper psychotherapeutic process [4]. It offers a contrast to the current use of medications and psychotherapy, which are often not well integrated and/or provided under the auspices of a single clinician. The fewer in number, but lengthier sessions in the presence of MDMA also redefine concepts regarding the appropriate approach and length of a therapy session involving engagement with traumatic material [5].

Working with FDA in America and the European Medicines Agency in Europe, the pooled data formed the basis for expansion into multi-site Phase 3 trials of MDMA therapy for PTSD. These are sponsored by a non-profit organization that has raised funds through philanthropy, which offers yet another model of drug and therapeutic development. Study centers in the United States are now underway. The European sites—in the Netherlands, United Kingdom, Germany, Finland, Portugal and the Czech Republic—are in the process of seeking approvals and are projected to start later in 2019, putting MDMA on course to becoming a licensed treatment in 2021 [6].

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