Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Behav Brain Res. Author manuscript; available in PMC 2021 July 15.

Published in final edited form as:

Behav Brain Res. 2020 July 15; 390: 112628. doi:10.1016/j.bbr.2020.112628.

Ketamine and rapid acting antidepressants: Are we ready to cure, rather than treat depression?

Chadi G. Abdallah[1,2,*], **John H. Krystal**[1,2]

[1]National Center for PTSD – Clinical Neuroscience Division, US Department of Veterans Affairs, West Haven, CT, USA

[2]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

Abstract

Depression is a leading cause of disability, with often chronic course of illness and high treatment resistance in a large proportion of patients. In the current short perspective paper, we present evidence supporting the presence of synaptic-based chronic stress pathology (CSP) in depression and across a number of psychiatric disorders. We summarize the synaptic connectivity model of CSP, and briefly review related preclinical and clinical evidence, while providing appropriate references for more comprehensive reviews and alternative models. We then underscore some gaps in the literature and provide various tips for future directions.

Keywords

Depression; antidepressants; ketamine; rapamycin; synaptic plasticity; relapse prevention

Introduction: Chronic Stress Pathology Appears to be a Common Pathway Across Several Disorders

Over the past few decades, it has become increasing evident that depression may share common pathways with several other psychiatric disorders. A key evidence is that slow acting antidepressants (SAADs), such as monoaminergic drugs, have shown some efficacy in treating major depressive disorder (MDD), bipolar depression, posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD), and several other pain and stress-related disorders [1–3]. This shared response among several disorders appears to also extend to rapid acting antidepressants (RAADs), with initial evidence supporting the efficacy of ketamine in depression and other stress-related disorders [4–6]. Importantly, both SAADs and RAADs are thought to induce therapeutic response by increasing neurotrophic factors and synaptogenesis, changes that are

[*]**Corresponding Author**: Chadi G. Abdallah, M.D.; Clinical Neuroscience Division – VA National Center for PTSD; Department of Psychiatry, Yale University School of Medicine; 950 Campbell Avenue 151 E, West Haven, Connecticut 06516; *Tel*: +1 (347) 987-0717; chadi.abdallah@yale.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

believed to reverse an underlying pathological synaptic loss (i.e., reduced density and strength) [7, 8]. Therefore, further supporting the presence of a common pathology is the fact that biological markers that are thought to reflect synaptic loss are also common across MDD, PTSD, GAD, and other stress-related disorders (e.g., prefrontal cortical thinning or hippocampal volume reduction) [9–18]. These disorders also share common biopsychosocial predisposing factors, from genetic variants to early life stress to trauma history. Additional supporting evidence of common pathology is the high co-morbidity and symptom overlap across these stress-related disorders [19].

These various lines of evidence are believed to be directly related to chronic stress pathology (CSP), a common feature across these neuropsychiatric disorders. Chronic stress could be a cause (e.g., traumatic event leading to MDD and/or PTSD), an outcome (e.g., prolonged suffering from GAD, OCD, or any of these stress-related disorders), or both (e.g., vicious cycle of trauma-PTSD) [20]. In this model, at least a subgroup of patients suffers from CSP, as manifested by regional synaptic dysconnectivity (i.e., loss and/or gain in density/strength) [8, 20].

The CSP model presents synaptic disruption in depression, as a converging pathway for various systems; including genetic/epigenetic predispositions, increased inflammation, HPA axis alterations, monoaminergic deficits and glutamatergic excitotoxicity [21]. These body systems were repeatedly implicated in the pathology and treatment of depression [8, 20, 21]. In our working model, abnormalities in these various systems converge on disrupting synaptic connectivity, which in turn affect brain circuitry and networks leading to symptoms of depression and other stress-related disorders [7, 8, 22]. The interaction between an individual biopsychosocial predisposition and their disease-inducing insults (e.g., inflammation, traumatic stress, etc.) results in differing patterns of synaptic dysconnectivity, which in turn translates in differing alterations in brain network and constellation of symptoms. For example, combat exposure, as an insult, may lead to PTSD, depression, or full recovery. In our model, the clinical presentation is the outcome of the specific brain network disruption [20, 22], which is in turn the result of the interaction between predisposition and disease-inducing insults.

Preclinical Evidence: Synaptic Connectivity is a Common Target for Treating Chronic Stress Pathology

Acute stress response appears to be beneficial to the brain and promotes resilience [23]. In contrast, chronic stress response have been repeatedly shown in animals to be detrimental to the brain and to lead to behavioral disturbances consistent with various symptoms observed in stress-related disorders [24, 25]. Well-replicated evidence demonstrated chronic stress-induced synaptic loss (density/strength) in the prefrontal cortex and hippocampus, as well as synaptic gain (density/strength) in the nucleus accumbens and basolateral amygdala [24, 26].

The synaptic loss is associated with amino-acid based pathology (ABP). ABP is thought to be triggered by stress-induced disturbance in amino-acid neurotransmission, consistent with increased extracellular glutamate leading to neuronal excitotoxicity. In animal studies, ABP was related to inefficient glutamate uptake by astrocytes, low glutamate and GABA (γ-

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

aminobutyric acid) neurotransmission, inactive brain derived neurotrophic factor (BDNF), dendritic shrinkage, and reduced synaptic density and strength. These ABP changes were also related to increased inflammation and impaired hypothalamic-pituitary-adrenal (HPA) axis [8, 20].

The synaptic gain is associated with monoamine-based pathology (MBP). MBP is believed to be the result of stress-induced monoaminergic transmission disturbance, with evidence showing increase dopamine as initial step in a cascade of events including co-release of BDNF leading to increased synaptogenesis in the nucleus accumbens. The magnitude and type of stressor appear to affect the nature of the monoaminergic disturbance. Additionally, only a subgroup of susceptible animals develops MBP following stress (reviewed in [8, 20]).

While individuals may have both ABP and MBP, extrapolating from the animal models of stress, it is predicted that a subpopulation of patients suffers from more prominent MBP [27, 28]. It is also believed that those who initially experience primarily MBP and synaptic gain may also later develop ABP due to the vicious cycle of untreated mental illness leading to chronic stress-induced synaptic loss, even in the amygdala and nucleus accumbens [20].

Clinical Evidence: Gray Matter Integrity and Functional Connectivity are Putative Markers of Synaptic Connectivity

Gray matter volumetric alterations in MDD and other stress-related disorders have long been interpreted as in vivo indicators of underlying synaptic loss or gain (i.e., density and strength) [29]. This hypothesis is supported by preclinical evidence directly relating synaptic density to regional brain volumes as measured by MRI [30]. More recently, accumulating evidence supported the presence of comparable association between functional global connectivity and each of synaptic density [31] and synaptic neurotransmission [32].

In stress-related disorders , there is well replicated evidence of reduced hippocampal volume and prefrontal cortical thickness [33, 34] putatively in the ABP subgroup, as well as pilot evidence of increased volume in the nucleus accumbens or amygdala [27, 35], presumably in the MBP subgroup. Notably, antidepressants appear to reverse this stress related gray matter alterations [27, 36, 37]. Similarly, convergent evidence supports the presence of altered functional global brain connectivity in MDD [32, 38–43] and in several psychiatric disorders with a considerable chronic stress component [11, 12, 39, 44–46]. Antidepressants, particularly ketamine, were shown to reverse this functional dysconnectivity [32, 36, 38, 47]. Together, these data highlight the potential utility of gray matter morphometry and functional connectivity as putative biomarkers of CSP. However, it is important to underscore that to-date these biomarkers were evident is some but not all studies, presumably due to methodological variabilities as well as ABP vs. MBP heterogeneity. Moreover, the individual effect size of these biomarkers is low, precluding their utility in clinical settings as univariate markers. It remains to be seen in future studies whether a biologically based stratification along with multivariate approaches would address the inconsistency and low effect size limitations.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Literature Gaps: Is it Time to Focus on Curing, rather than Treating Chronic Stress Pathology?

Are we ready to cure rather than treat depression? Unfortunately, the answer is we are not there yet and much work is still needed. Ketamine and other RAADs were found to normalize the stress-induced synaptic dysconnectivity in animals, showing both prefrontal synaptic gain and nucleus accumbens synaptic loss within 24h of treatment [48, 49]. Yet, these synaptic normalization effects are thought to be transient and relapse within 10 days [50]. Similarly, early human studies showed rapid normalization of functional connectivity, as well increased hippocampal but reduced nucleus accumbens volumes within 24h of successful ketamine treatment [27, 32, 38, 47]. These neurobiological changes are accompanied by RAAD effects. Unfortunately, patients also often relapse within 1–2 weeks of single treatment [51].

A major gap of preclinical literature is the lack of focus on the molecular basis of post-ketamine relapse. Understanding the biological relapse mechanisms may unravel new approaches that ultimately could help curing, rather than simply treating depression. Current clinical standards are to administer ketamine repeatedly to maintain response, e.g., twice per week in the induction phase. Neurobiologically, the relapse in symptoms is thought to be due to reversal of ketamine-induced synaptic normalization, although confirmatory data are scarce. Investigating the reversibility of treatment-related synaptic changes is essential to truly understand the etiological mechanisms triggering and sustaining depression. Unfortunately, the neurobiological literature has been largely limited to the acute effects of ketamine within 24h. Few state-of-the-art studies examined the effects of ketamine up to 2 weeks [52, 53]. However, these studies discontinued the “insults” (cortisone or stress) following ketamine treatment. Here, it is important to note that there is extensive evidence supporting the reversibility of stress-induced synaptic loss in these otherwise normal animals, often within weeks of withholding the insults [23, 24]. Therefore, to model human depression and the rapid relapse after single ketamine infusion, future studies should maintain the insult (e.g., stress or cortisol) and investigate the processes involved in the synaptogenic relapse. Equally important, studies investigating the mechanisms underlying the reversibility of stress-induced synaptic loss may also provide clues to the etiology of depression and perhaps assist in providing a cure.

Another related gap is that many of the elegant preclinical studies have conducted the bulk [54, 55] or all [56, 57] of their behavioral assessment of the antidepressant-like effects within few hours of ketamine administration, a period during which the animal may still be under the influence of ketamine and its metabolites. More importantly, these acute effects do not model the clinically meaningful antidepressant effects of ketamine, which are sustained for 1–7 days. The limitations of the “depression under influence” data are twofold, 1) the biological results may include non-specific ketamine effects that are not relevant to its RAAD effects in humans, and 2) the examined behavioral outcomes may be affected by the intoxication, rather than the sustained antidepressant properties. In our view, the clinical relevance of any antidepressant effects during intoxication is highly questionable. Therefore,

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

we believe future preclinical studies would benefit from collecting data at least 24h post administration, when ketamine has been fully metabolized.

The above-mentioned gaps are not just limited to preclinical studies, human research is also lagging in conducting interventional mechanistic studies. To date, the majority of human biological studies are observational in nature, where biomarkers are acquired before, during, or after treatment. These studies are more informative than cross-sectional investigations, but the evidence remains correlational in nature. To provide causal evidence, the field should aim for interventional mechanistic studies, particularly those that are focusing on translating the preclinical-based models to humans, as well those that attempt to unravel the mechanisms of relapse. Comparable studies have been conducted in healthy volunteers, e.g., pretreatment with the glutamate inhibitor lamotrigine to ascertain the causal relationship between glutamate neurotransmission and the ketamine-induced global brain connectivity [32]. The value of this type of studies is highlighted by the fact that the RAAD effects of ketamine were initially demonstrated through an interventional mechanistic study [58]. More recently, another interventional mechanistic study in depressed patients discovered that pretreatment with the immunosuppressant rapamycin significantly prolongs the response to ketamine, while demonstrating the inability of systemic inhibition of the mechanistic target of rapamycin (mTOR) to block the acute RAAD effects [51]. Compared to placebo pretreatment, one oral dose of rapamycin tripled the response rates and quadrupled remission rates at 2 weeks post single ketamine infusion [51]. Both studies may be considered high-risk high-grain or difficult to fund and/or conduct. They are also pilot in nature and more suitable for exploring neurobiological models, than for confirming clinical efficacy of a treatment; therefore, replication is essential. Yet, these studies underscore the need for investigating preclinical models in humans and highlight the unexpected findings that resulted from careful assessment of brain mechanisms. The ketamine mechanistic discovery study [58] opened the door for a number of confirmatory clinical studies [59] and a wealth of preclinical back translation opportunities to gain new insight into the biology and treatment of depression [60, 61]. It is hoped that the rapamycin results [51] would successfully replicate in humans and that their back translation to animal studies will help identifying the etiological mechanisms of relapse and, ultimately provides new approaches for curing depression. Similarly, a recent mechanistic human study demonstrated a previously unknown role for opioid modulation for successful ketamine treatment [62]. The field would benefit from more clinical mechanistic studies, particularly if those were accompanied with biological assessment of target engagement.

Conclusion: The Brain Works in Mysterious Ways

Tremendous progress has been achieved in terms of gaining new knowledge and having better understanding of the putative mechanisms of CSP, and subsequently depression and other stress-related disorders. Yet, a large part of this knowledge remains tilted toward preclinical evidence with sparse but reproducible suggestive human findings.

Biological signatures of depression have been reported in human studies from neuroimaging biomarkers to omics evidence. However, the reproducibility, the specificity, the effect size, and the ubiquity of these findings across all depressed patients have often been challenging.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

In general, the biological revolution in psychiatric research has not yet fully translated into clinical biomarkers of diagnosis, of disease progress, or even of treatment targets. The main clinically relevant success was in terms of biological treatments. Yet, the biological treatments currently used in clinics are mostly the product of serendipity followed by development of new drugs with comparable molecular mechanism of action. Unfortunately, this approach has worked for SAAD, but failed repeatedly with RAAD (e.g., lanicemine and rapastinel). To date, successful rational drug development pipelines remains the exception (e.g. brexanolone), rather than the rule (e.g., mGluRs).

Taking notes of the progress made and potential shortcomings of our approach to clinical neuroscience, below are few suggestions that may expedite our journey towards ultimately curing depression and other mental illnesses:

1. We should underscore the urgent need for clinically useful products, particularly biomarkers of treatment targets and disease progress. The literature is full of storytelling papers, yet the findings are not always easy to replicate and if they do, their effect size is often too small to be clinically meaningful. For example, the association between depression and hippocampal volume is reproducible, but it is neither robust (i.e., not consistently evident in small samples) nor specific (i.e., shared with most psychiatric disorder) [63]. The clinical neuroscience field has generated incomprehensible number of findings, it is time to attend to integrating them into knowledge and to prioritize producing clinical products over generating more stories (e.g., focusing on the robustness and reproducibility of identified biomarkers).

2. We should expand the research portfolio beyond cross sectional investigations in small cohorts (e.g., n < 100 subjects per group). After seven decades of biological research, it is becoming increasingly evident that a single genetic (e.g., serotonin transporter polymorphism), anatomical (e.g., hippocampal volume), functional (e.g., amygdala activity or connectivity), or molecular pathology (e.g., low serotonin or high glutamate) is unlikely to fully or even meaningfully account for the neurobiology of clinical depression; or for that matter any other neuropsychiatric disorder. We should aim to concurrently target multiple markers and embrace multivariate pattern analyses along with predictive models and network approaches, while reducing our reliance on univariate interpretive statistics. Machine learning approaches combined with large data collection have made substantial progress in other fields. It is our hope that clinically informed features engineering and integration of these new tools would lead to new biomarkers and novel treatments (e.g., [36]).

3. We should encourage longitudinal studies – regardless of sample size, particularly interventional mechanistic investigations that may provide causal evidence rather than simple correlations. The field of clinical neuroscience research is full of associative evidence, it is now time to conduct the high-risk high-gain human studies. Basic studies are indispensable. However, the generated preclinical models are considered putative and should be demonstrated in humans. Inference across species is at best speculative and the literature is full

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

of examples where these models do not hold true in humans; e.g., recent failure of rapastinel in human studies, despite achieving all preclinical targets both biologically and behaviorally [64]. Human mechanistic studies, accompanied with assessment of target engagement, may be difficult to do, but they are necessary if we are to make two-ways translational progress.

4. While not all unexpected findings will replicate, history has taught us the value and impact of careful assessment of evidence and readiness to rigorously pursue new directions. From penicillin to tricyclic antidepressants, progress in medicine, especially in psychiatry, has been full of examples where serendipity combined with astute clinical research have led to novel treatments and greater understanding of underlying pathology.

5. Call it as it is. Preclinically, if chronic stress produces synaptic loss, then let's not label it depression or PTSD. Clinically, if hippocampal volume reduction is neither sensitive (approximately 1% less than control), nor specific (evident in MDD and PTSD, among other disorders), then let's not call it a biomarker of MDD or PTSD [63]. These behavior-first approaches, where the biological correlates are investigated, have not yielded much biological research progress. Perhaps it is time to aim for a biology-first approach, where the behavioral correlates of a biological disturbance are investigated. Psychiatric diagnoses served an important clinical purpose. Rather than inventing an alternative behavior-first approach, such as RDoC, it may be time to create from the ground up a novel biology-first approach designed specifically for clinical neuroscience.

Funding and Disclosure

Funding support was provided by NIMH (K23MH101498), and the VA National Center for PTSD. The content of this report is solely the responsibility of the authors and does not necessarily represent the official views of the sponsors, the Department of Veterans Affairs, NIH, or the U.S. Government.

Dr. Abdallah has served as a consultant, speaker and/or on advisory boards for Genentech, Janssen, Psilocybin Labs, Lundbeck and FSV7, and editor of *Chronic Stress* for Sage Publications, Inc.; Filed a patent for using mTORC1 inhibitors to augment the effects of antidepressants (filed on Aug 20, 2018). Dr. Krystal is a consultant for AbbVie, Inc., Amgen, Astellas Pharma Global Development, Inc., AstraZeneca Pharmaceuticals, Biomedisyn Corporation, Bristol-Myers Squibb, Eli Lilly and Company, Euthymics Bioscience, Inc., Neurovance, Inc., FORUM Pharmaceuticals, Janssen Research & Development, Lundbeck Research USA, Novartis Pharma AG, Otsuka America Pharmaceutical, Inc., Sage Therapeutics, Inc., Sunovion Pharmaceuticals, Inc., and Takeda Industries; is on the Scientific Advisory Board for Lohocla Research Corporation, Mnemosyne Pharmaceuticals, Inc., Naurex, Inc., and Pfizer; is a stockholder in Biohaven Pharmaceuticals; holds stock options in Mnemosyne Pharmaceuticals, Inc.; holds patents for Dopamine and Noradrenergic Reuptake Inhibitors in Treatment of Schizophrenia, U.S. Patent No. 5,447,948 (issued Sep 5, 1995), and Glutamate Modulating Agents in the Treatment of Mental Disorders, U.S. Patent No. 8,778,979 (issued Jul 15, 2014); and filed a patent for Intranasal Administration of Ketamine to Treat Depression - U.S. Application No. 14/197,767 (filed on Mar 5, 2014); U.S. application or Patent Cooperation Treaty international application No. 14/306,382 (filed on Jun 17, 2014). Filed a patent for using mTORC1 inhibitors to augment the effects of antidepressants (filed on Aug 20, 2018).

Uncommon Abbreviations:

ABP	amino acid-based pathology
CSP	chronic stress pathology
MBP	monoamine-based pathology

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

RAAD	rapid acting antidepressant
SAAD	slow acting antidepressant

References

[1]. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, Leucht S, Ruhe HG, Turner EH, Higgins JPT, Egger M, Takeshima N, Hayasaka Y, Imai H, Shinohara K, Tajika A, Ioannidis JPA, Geddes JR, Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis, Lancet 391(10128) (2018) 1357–1366. [PubMed: 29477251]

[2]. Cipriani A, Williams T, Nikolakopoulou A, Salanti G, Chaimani A, Ipser J, Cowen PJ, Geddes JR, Stein DJ, Comparative efficacy and acceptability of pharmacological treatments for post-traumatic stress disorder in adults: a network meta-analysis, Psychol Med (2017) 1–10.

[3]. Helfer B, Samara MT, Huhn M, Klupp E, Leucht C, Zhu Y, Engel RR, Leucht S, Efficacy and Safety of Antidepressants Added to Antipsychotics for Schizophrenia: A Systematic Review and Meta-Analysis, Am J Psychiatry 173(9) (2016) 876–86. [PubMed: 27282362]

[4]. Feder A, Parides MK, Murrough JW, Perez AM, Morgan JE, Saxena S, Kirkwood K, Aan Het Rot M, Lapidus KA, Wan LB, Iosifescu D, Charney DS, Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial, JAMA psychiatry 71(6) (2014) 681–8. [PubMed: 24740528]

[5]. Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM, Iqbal S, Pillemer S, Foulkes A, Shah A, Charney DS, Mathew SJ, Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial, Am J Psychiatry 170(10) (2013) 1134–42. [PubMed: 23982301]

[6]. Taylor JH, Landeros-Weisenberger A, Coughlin C, Mulqueen J, Johnson JA, Gabriel D, Reed MO, Jakubovski E, Bloch MH, Ketamine for Social Anxiety Disorder: A Randomized, Placebo-Controlled Crossover Trial, Neuropsychopharmacology 43(2) (2018) 325–333. [PubMed: 28849779]

[7]. Abdallah CG, Sanacora G, Duman RS, Krystal JH, Ketamine and rapid-acting antidepressants: a window into a new neurobiology for mood disorder therapeutics, Annu Rev Med 66 (2015) 509–23. [PubMed: 25341010]

[8]. Abdallah CG, Sanacora G, Duman RS, Krystal JH, The neurobiology of depression, ketamine and rapid-acting antidepressants: Is it glutamate inhibition or activation?, Pharmacol Ther 190 (2018) 148–158. [PubMed: 29803629]

[9]. Abdallah CG, Coplan JD, Jackowski A, Sato JR, Mao X, Shungu DC, Mathew SJ, A pilot study of hippocampal volume and N-acetylaspartate (NAA) as response biomarkers in riluzole-treated patients with GAD, Eur Neuropsychopharmacol 23(4) (2013) 276–84. [PubMed: 22739126]

[10]. Kwon JS, Shin YW, Kim CW, Kim YI, Youn T, Han MH, Chang KH, Kim JJ, Similarity and disparity of obsessive-compulsive disorder and schizophrenia in MR volumetric abnormalities of the hippocampus-amygdala complex, J Neurol Neurosurg Psychiatry 74(7) (2003) 962–4. [PubMed: 12810792]

[11]. Anticevic A, Brumbaugh MS, Winkler AM, Lombardo LE, Barrett J, Corlett PR, Kober H, Gruber J, Repovs G, Cole MW, Krystal JH, Pearlson GD, Glahn DC, Global prefrontal and fronto-amygdala dysconnectivity in bipolar I disorder with psychosis history, Biol Psychiatry 73(6) (2013) 565–73. [PubMed: 22980587]

[12]. Anticevic A, Hu S, Zhang S, Savic A, Billingslea E, Wasylink S, Repovs G, Cole MW, Bednarski S, Krystal JH, Bloch MH, Li CS, Pittenger C, Global resting-state functional magnetic resonance imaging analysis identifies frontal cortex, striatal, and cerebellar dysconnectivity in obsessive-compulsive disorder, Biol Psychiatry 75(8) (2014) 595–605. [PubMed: 24314349]

[13]. Haukvik UK, Westlye LT, Morch-Johnsen L, Jorgensen KN, Lange EH, Dale AM, Melle I, Andreassen OA, Agartz I, In vivo hippocampal subfield volumes in schizophrenia and bipolar disorder, Biol Psychiatry 77(6) (2015) 581–8. [PubMed: 25127742]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

[14]. Syed SA, Nemeroff CB, Early Life Stress, Mood, and Anxiety Disorders, Chronic Stress 1 (2017) 2470547017694461.

[15]. Matosin N, Cruceanu C, Binder EB, Preclinical and Clinical Evidence of DNA Methylation Changes in Response to Trauma and Chronic Stress, Chronic Stress 1 (2017) 2470547017710764.

[16]. Sheth C, McGlade E, Yurgelun-Todd D, Chronic Stress in Adolescents and Its Neurobiological and Psychopathological Consequences: An RDoC Perspective, Chronic Stress 1 (2017) 2470547017715645.

[17]. Adams TG, Kelmendi B, Brake CA, Gruner P, Badour CL, Pittenger C, The Role of Stress in the Pathogenesis and Maintenance of Obsessive-Compulsive Disorder, Chronic Stress 2 (2018) 2470547018758043.

[18]. Goddard AW, The Neurobiology of Panic: A Chronic Stress Disorder, Chronic Stress 1 (2017) 2470547017736038. [PubMed: 32440580]

[19]. Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU, Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States, Int J Methods Psychiatr Res 21(3) (2012) 169–84. [PubMed: 22865617]

[20]. Abdallah CG, Averill LA, Akiki TJ, Raza M, Averill CL, Gomaa H, Adikey A, Krystal JH, The Neurobiology and Pharmacotherapy of Posttraumatic Stress Disorder, Annu Rev Pharmacol Toxicol 59 (2019) 171–189. [PubMed: 30216745]

[21]. Haroon E, Miller AH, Sanacora G, Inflammation, Glutamate, and Glia: A Trio of Trouble in Mood Disorders, Neuropsychopharmacology 42(1) (2017) 193–215. [PubMed: 27629368]

[22]. Akiki TJ, Averill CL, Abdallah CG, A Network-Based Neurobiological Model of PTSD: Evidence From Structural and Functional Neuroimaging Studies, Curr Psychiatry Rep 19(11) (2017) 81. [PubMed: 28924828]

[23]. Popoli M, Yan Z, McEwen BS, Sanacora G, The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission, Nat Rev Neurosci 13(1) (2012) 22–37.

[24]. McEwen BS, Neurobiological and Systemic Effects of Chronic Stress, Chronic Stress 1 (2017) 1–11.

[25]. McEwen BS, What Is the Confusion With Cortisol?, Chronic Stress 3 (2019) 2470547019833647.

[26]. Russo SJ, Nestler EJ, The brain reward circuitry in mood disorders, Nat Rev Neurosci 14(9) (2013) 609–25. [PubMed: 23942470]

[27]. Abdallah CG, Jackowski A, Salas R, Gupta S, Sato JR, Mao X, Coplan JD, Shungu DC, Mathew SJ, The Nucleus Accumbens and Ketamine Treatment in Major Depressive Disorder, Neuropsychopharmacology 42(8) (2017) 1739–1746. [PubMed: 28272497]

[28]. Abdallah CG, Jackowski A, Sato JR, Mao X, Kang G, Cheema R, Coplan JD, Mathew SJ, Shungu DC, Prefrontal cortical GABA abnormalities are associated with reduced hippocampal volume in major depressive disorder, Eur Neuropsychopharmacol 25(8) (2015) 1082–90. [PubMed: 25983019]

[29]. Drevets WC, Price JL, Furey ML, Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression, Brain Struct Funct 213(1–2) (2008) 93–118. [PubMed: 18704495]

[30]. Kassem MS, Lagopoulos J, Stait-Gardner T, Price WS, Chohan TW, Arnold JC, Hatton SN, Bennett MR, Stress-induced grey matter loss determined by MRI is primarily due to loss of dendrites and their synapses, Molecular neurobiology 47(2) (2013) 645–61. [PubMed: 23138690]

[31]. Holmes SE, Scheinost D, Finnema SJ, Naganawa M, Davis MT, DellaGioia N, Nabulsi N, Matuskey D, Angarita GA, Pietrzak RH, Duman RS, Sanacora G, Krystal JH, Carson RE, Esterlis I, Lower synaptic density is associated with depression severity and network alterations, Nat Commun 10(1) (2019) 1529. [PubMed: 30948709]

[32]. Abdallah CG, Averill CL, Salas R, Averill LA, Baldwin PR, Krystal JH, Mathew SJ, Mathalon DH, Prefrontal Connectivity and Glutamate Transmission: Relevance to Depression Pathophysiology and Ketamine Treatment, Biol Psychiatry Cogn Neurosci Neuroimaging 2(7) (2017) 566–574. [PubMed: 29034354]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

[33]. Logue MW, van Rooij SJH, Dennis EL, Davis SL, Hayes JP, Stevens JS, Densmore M, Haswell CC, Ipser J, Koch SBJ, Korgaonkar M, Lebois LAM, Peverill M, Baker JT, Boedhoe PSW, Frijling JL, Gruber SA, Harpaz-Rotem I, Jahanshad N, Koopowitz S, Levy I, Nawijn L, O'Connor L, Olff M, Salat DH, Sheridan MA, Spielberg JM, van Zuiden M, Winternitz SR, Wolff JD, Wolf EJ, Wang X, Wrocklage K, Abdallah CG, Bryant RA, Geuze E, Jovanovic T, Kaufman ML, King AP, Krystal JH, Lagopoulos J, Bennett M, Lanius R, Liberzon I, McGlinchey RE, McLaughlin KA, Milberg WP, Miller MW, Ressler KJ, Veltman DJ, Stein DJ, Thomaes K, Thompson PM, Morey RA, Smaller Hippocampal Volume in Posttraumatic Stress Disorder: A Multisite ENIGMA-PGC Study: Subcortical Volumetry Results From Posttraumatic Stress Disorder Consortia, Biol Psychiatry 83(3) (2018) 244–253. [PubMed: 29217296]

[34]. Schmaal L, Veltman DJ, van Erp TG, Samann PG, Frodl T, Jahanshad N, Loehrer E, Tiemeier H, Hofman A, Niessen WJ, Vernooij MW, Ikram MA, Wittfeld K, Grabe HJ, Block A, Hegenscheid K, Volzke H, Hoehn D, Czisch M, Lagopoulos J, Hatton SN, Hickie IB, Goya-Maldonado R, Kramer B, Gruber O, Couvy-Duchesne B, Renteria ME, Strike LT, Mills NT, de Zubicaray GI, McMahon KL, Medland SE, Martin NG, Gillespie NA, Wright MJ, Hall GB, MacQueen GM, Frey EM, Carballedo A, van Velzen LS, van Tol MJ, van der Wee NJ, Veer IM, Walter H, Schnell K, Schramm E, Normann C, Schoepf D, Konrad C, Zurowski B, Nickson T, McIntosh AM, Papmeyer M, Whalley HC, Sussmann JE, Godlewska BR, Cowen PJ, Fischer FH, Rose M, Penninx BW, Thompson PM, Hibar DP, Subcortical brain alterations in major depressive disorder: findings from the ENIGMA Major Depressive Disorder working group, Mol Psychiatry 21(6) (2016) 806–12. [PubMed: 26122586]

[35]. Kuo JR, Kaloupek DG, Woodward SH, Amygdala volume in combat-exposed veterans with and without posttraumatic stress disorder: a cross-sectional study, Arch Gen Psychiatry 69(10) (2012) 1080–6. [PubMed: 23026958]

[36]. Nemati S, Akiki TJ, Roscoe J, Ju Y, Averill CL, Fouda S, Dutta A, McKie S, Krystal JH, Deakin JFW, Averill LA, Abdallah CG, A Unique Brain Connectome Fingerprint Predates and Predicts Response to Antidepressants, iScience 23(1) (2020) 100800. [PubMed: 31918047]

[37]. Oltedal L, Narr KL, Abbott C, Anand A, Argyelan M, Bartsch H, Dannlowski U, Dols A, van Eijndhoven P, Emsell L, Erchinger VJ, Espinoza R, Hahn T, Hanson LG, Hellemann G, Jorgensen MB, Kessler U, Oudega ML, Paulson OB, Redlich R, Sienaert P, Stek ML, Tendolkar I, Vandenbulcke M, Oedegaard KJ, Dale AM, Volume of the Human Hippocampus and Clinical Response Following Electroconvulsive Therapy, Biol Psychiatry 84(8) (2018) 574–581. [PubMed: 30006199]

[38]. Abdallah CG, Averill LA, Collins KA, Geha P, Schwartz J, Averill C, DeWilde KE, Wong E, Anticevic A, Tang CY, Iosifescu DV, Charney DS, Murrough JW, Ketamine Treatment and Global Brain Connectivity in Major Depression, Neuropsychopharmacology 42(6) (2017) 1210–1219. [PubMed: 27604566]

[39]. Holmes SE, Scheinost D, DellaGioia N, Davis MT, Matuskey D, Pietrzak RH, Hampson M, Krystal JH, Esterlis I, Cerebellar and prefrontal cortical alterations in PTSD: structural and functional evidence, Chronic Stress 2 (2018).

[40]. Murrough JW, Abdallah CG, Anticevic A, Collins KA, Geha P, Averill LA, Schwartz J, DeWilde KE, Averill C, Jia-Wei Yang G, Wong E, Tang CY, Krystal JH, Iosifescu DV, Charney DS, Reduced global functional connectivity of the medial prefrontal cortex in major depressive disorder, Hum Brain Mapp 37(9) (2016) 3214–23. [PubMed: 27144347]

[41]. Scheinost D, Holmes SE, DellaGioia N, Schleifer C, Matuskey D, Abdallah CG, Hampson M, Krystal JH, Anticevic A, Esterlis I, Multimodal Investigation of Network Level Effects Using Intrinsic Functional Connectivity, Anatomical Covariance, and Structure-to-Function Correlations in Unmedicated Major Depressive Disorder, Neuropsychopharmacology 43(5) (2018) 1119–1127. [PubMed: 28944772]

[42]. Wang L, Dai Z, Peng H, Tan L, Ding Y, He Z, Zhang Y, Xia M, Li Z, Li W, Cai Y, Lu S, Liao M, Zhang L, Wu W, He Y, Li L, Overlapping and segregated resting-state functional connectivity in patients with major depressive disorder with and without childhood neglect, Hum Brain Mapp 35(4) (2014) 1154–66. [PubMed: 23408420]

[43]. Kraus C, Mkrtchian A, Kadriu B, Nugent AC, Zarate CA Jr., Evans JW, Evaluating global brain connectivity as an imaging marker for depression: influence of preprocessing strategies and placebo-controlled ketamine treatment, Neuropsychopharmacology (2020).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

[44]. Abdallah CG, Averill CL, Ramage AE, Averill LA, Goktas S, Nemati S, Krystal JH, Roache JD, Resick PA, Young-McCaughan S, Peterson AL, Fox P, Consortium SS, Salience Network Disruption in U.S. Army Soldiers With Posttraumatic Stress Disorder, Chronic Stress 3 (2019) 2470547019850467.

[45]. Abdallah CG, Averill CL, Ramage AE, Averill LA, Alkin E, Nemati S, Krystal JH, Roache JD, Resick P, Young-McCaughan S, Peterson AL, Fox P, Reduced Salience and Enhanced Central Executive Connectivity Following PTSD Treatment, Chronic Stress 3 (2019) 2470547019838971.

[46]. Abdallah CG, Wrocklage KM, Averill CL, Akiki T, Schweinsburg B, Roy A, Martini B, Southwick SM, Krystal JH, Scott JC, Anterior hippocampal dysconnectivity in posttraumatic stress disorder: a dimensional and multimodal approach, Translational psychiatry 7(2) (2017) e1045. [PubMed: 28244983]

[47]. Abdallah CG, Dutta A, Averill CL, McKie S, Akiki TJ, Averill LA, William Deakin J, Ketamine, but Not the NMDAR Antagonist Lanicemine, Increases Prefrontal Global Connectivity in Depressed Patients, Chronic Stress 2 (2018) 2470547018796102.

[48]. Li N, Liu RJ, Dwyer JM, Banasr M, Lee B, Son H, Li XY, Aghajanian G, Duman RS, Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure, Biol Psychiatry 69(8) (2011) 754–61. [PubMed: 21292242]

[49]. Reus GZ, Abelaira HM, dos Santos MA, Carlessi AS, Tomaz DB, Neotti MV, Liranco JL, Gubert C, Barth M, Kapczinski F, Quevedo J, Ketamine and imipramine in the nucleus accumbens regulate histone deacetylation induced by maternal deprivation and are critical for associated behaviors, Behav Brain Res 256 (2013) 451–6. [PubMed: 24004850]

[50]. Duman RS, Aghajanian GK, Synaptic dysfunction in depression: potential therapeutic targets, Science 338(6103) (2012) 68–72. [PubMed: 23042884]

[51]. Abdallah CG, Averill LA, Gueorguieva R, Goktas S, Purohit P, Ranganathan M, Sherif M, Ahn KH, D'Souza DC, Formica R, Southwick SM, Duman RS, Sanacora G, Krystal J, Modulation of the Antidepressant Effects of Ketamine by the mTORC1 Inhibitor Rapamycin, Neuropsychopharmacology (2020).

[52]. Moda-Sava RN, Murdock MH, Parekh PK, Fetcho RN, Huang BS, Huynh TN, Witztum J, Shaver DC, Rosenthal DL, Alway EJ, Lopez K, Meng Y, Nellissen L, Grosenick L, Milner TA, Deisseroth K, Bito H, Kasai H, Liston C, Sustained rescue of prefrontal circuit dysfunction by antidepressant-induced spine formation, Science 364(6436) (2019).

[53]. Phoumthipphavong V, Barthas F, Hassett S, Kwan AC, Longitudinal Effects of Ketamine on Dendritic Architecture In Vivo in the Mouse Medial Frontal Cortex, eNeuro 3(2) (2016).

[54]. Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng PF, Kavalali ET, Monteggia LM, NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses, Nature 475(7354) (2011) 91–5 LID - 10.1038/nature10130 [doi]. [PubMed: 21677641]

[55]. Zanos P, Moaddel R, Morris PJ, Georgiou P, Fischell J, Elmer GI, Alkondon M, Yuan P, Pribut HJ, Singh NS, Dossou KS, Fang Y, Huang XP, Mayo CL, Wainer IW, Albuquerque EX, Thompson SM, Thomas CJ, Zarate CA Jr., Gould TD, NMDAR inhibition-independent antidepressant actions of ketamine metabolites, Nature 533(7604) (2016) 481–6. [PubMed: 27144355]

[56]. Li SX, Han Y, Xu LZ, Yuan K, Zhang RX, Sun CY, Xu DF, Yuan M, Deng JH, Meng SQ, Gao XJ, Wen Q, Liu LJ, Zhu WL, Xue YX, Zhao M, Shi J, Lu L, Uncoupling DAPK1 from NMDA receptor GluN2B subunit exerts rapid antidepressant-like effects, Mol Psychiatry 23(3) (2018) 597–608. [PubMed: 28439098]

[57]. Yang Y, Cui Y, Sang K, Dong Y, Ni Z, Ma S, Hu H, Ketamine blocks bursting in the lateral habenula to rapidly relieve depression, Nature 554(7692) (2018) 317–322. [PubMed: 29446381]

[58]. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH, Antidepressant effects of ketamine in depressed patients, Biol Psychiatry 47(4) (2000) 351–4. [PubMed: 10686270]

[59]. Kraus C, Wasserman D, Henter ID, Acevedo-Diaz E, Kadriu B, Zarate CA Jr., The influence of ketamine on drug discovery in depression, Drug Discov Today (2019).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

[60]. Hare B, Ghosal S, Duman R, Rapid acting antidepressants in chronic stress models: molecular and cellular mechanisms, Chronic Stress 1 (2017) 1–16.

[61]. Zanos P, Thompson SM, Duman RS, Zarate CA Jr., Gould TD, Convergent Mechanisms Underlying Rapid Antidepressant Action, CNS Drugs 32(3) (2018) 197–227. [PubMed: 29516301]

[62]. Williams NR, Heifets BD, Blasey C, Sudheimer K, Pannu J, Pankow H, Hawkins J, Birnbaum J, Lyons DM, Rodriguez CI, Schatzberg AF, Attenuation of Antidepressant Effects of Ketamine by Opioid Receptor Antagonism, Am J Psychiatry 175(12) (2018) 1205–1215. [PubMed: 30153752]

[63]. Gosnell S, Meyer M, Jennings C, Ramirez D, Schmidt J, Oldham J, Salas R, Hippocampal volume in psychiatric diagnoses: Should psychiatry biomarker research account for comorbidities?, Chronic Stress 4 (2020) 2470547020906799. [PubMed: 32440605]

[64]. Liu RJ, Duman C, Kato T, Hare B, Lopresto D, Bang E, Burgdorf J, Moskal J, Taylor J, Aghajanian G, Duman RS, GLYX-13 Produces Rapid Antidepressant Responses with Key Synaptic and Behavioral Effects Distinct from Ketamine, Neuropsychopharmacology 42(6) (2017) 1231–1242. [PubMed: 27634355]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Highlights

- Chronic stress pathology (CSP) is characterized by patterns of synaptic dysconnectivity
- CSP dysconnectivity is reversible within a month of discontinuing stress in rodents
- The effects of ketamine on CSP dysconnectivity are also short lived
- The field should focus on the reversibility of these synaptic changes
- Mechanisms of CSP reversibility may unravel new approaches toward curing depression