Aus dem Institut für Affektive Neurowissenschaften und Emotionsmodulation der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Investigation of the effects of a single sub-anaesthetic ketamine infusion on symptoms of major depressive disorder and their association with neural activation patterns in cognition-emotion related brain areas

Die Untersuchung der Effekte einer einzelnen subanästhetischen Ketamininfusion auf Symptome der Major Depression und ihr Zusammenhang mit neuralen Aktivierungsmustern in Kognitions- und Emotions-assoziierten Gehirnarealen

zur Erlangung des akademischen Grades
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von

Anna Stippl

aus Baden-Baden

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List of Abbreviations

ACC	Anterior cingulate cortex
AInsula	Anterior insula
AM	Amygdala
AN	Affective network
ANCOVA	Analysis of covariance
BAWL	Berlin affective word list
BDI	Beck depression inventory
BDNF	Brain-derived neurotrophic factor
BOLD	Blood oxygenation level-dependent
CCN	Cognitive control network
CHAR	Charité Universitätsmedizin Berlin
DLPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
DMPFC	Dorsomedial prefrontal cortex
fMRI	Functional magnetic resonance imaging
HAMD	Hamilton depression rating scale
IPL	Inferior parietal lobule
ITG	Inferior temporal gyrus
lDLPFC	Dorsolateral prefrontal cortex
M	Mean
MADRS	Montgomery asberg depression rating scale
MAO inhibitors	Monoamine oxidase inhibitors
MDD	Major depressive disorder
MNI	Montreal neurological institute
NMDA-R	N-methyl-D-aspartate glutamate receptor

PCB	Percent change to baseline
PCC	Posterior cingulate cortex
pgACC	Pregenual anterior cingulate cortex
PostCG	Postcentral gyrus
PreCG	Precentral gyrus
ROI	Region of interest
SD	Standard Deviation
sgACC	Subgenual anterior cingulate cortex
SSNRI’s	Selective serotonin noradrenaline reuptake inhibitors
SSRI’s	Selective serotonin reuptake inhibitors
TCAs	Tricyclic antidepressants
TRD	Treatment resistant depressive
UZH	University of Zurich
VMPFC	Ventromedial prefrontal cortex
WM	Working memory

1. Abstract (English)

Background: Major Depressive Disorder (MDD) is still regarded as often difficult to treat due to its large variety in symptoms. Ketamine has demonstrated rapid antidepressant effects, already 24 h after a single subanaesthetic infusion, but is still lacking effective predictors for a positive treatment response.

Objectives: The primary goal of this dissertation project was to investigate ketamine's effect on distinct MDD symptom dimensions (i.e. cognitive, affective and somatic). Furthermore, by applying a working memory (WM) related functional Magnetic Resonance Imaging (fMRI) paradigm, this project focused on the detection of MDD symptom specific response predictors.

Methods: We implemented a symptom-based approach by utilizing a three-factor solution of the Beck Depression Inventory (BDI) in a sample of 47 MDD patients 24 hours pre- and post- a single ketamine infusion. Subsequently, we accessed functional activity at baseline in correlation with MDD symptom improvements 24 h post-treatment in a subsample of 16 patients. Since aberrant functional activation in the default mode network (DMN) and the dorsolateral prefrontal cortex (DLPFC) has been associated with dysfunctional cognition-emotion interaction in MDD, we focused on the examination of these brain regions.

Results: On the behavioral level our results indicated that ketamine influences MDD symptom dimensions to a different extent, whereby predominantly affecting the cognitive domain. On the neural level, we found evidence that a decreased DMN deactivation and elevated DLPFC activation predicts ketamine's enhanced effect on cognitive symptoms.

Conclusion: Taken together, these findings suggest that ketamine's antidepressant efficacy is driven by a "pro-cognitive mechanism" that might be substantiated by an elevated capability for "adaptive adjustment" in the described functional networks.

2. Abstract (German)

Hintergrund: Die Major Depression (MDD) gilt aufgrund ihrer großen Symptomvielfalt noch immer als häufig schwer zu behandeln. Ketamin zeigt bereits 24 h nach einer einzelnen subanästhetischen Infusion eine schnelle antidepressive Wirkung, wobei es weiterhin an wirksamen Prädiktoren für ein positives Ansprechen auf die Behandlung mangelt.

Ziel: Das primäre Ziel dieses Dissertationsprojekts bestand darin, die Wirkung von Ketamin auf verschiedene MDD-Symptomdimensionen (d.h. kognitiv, affektiv und somatisch) zu untersuchen. Überdies lag der Fokus des Projektes darauf, durch die Anwendung eines Arbeitsgedächtnis-assoziierten funktionellen Magnetresonanztomographie (fMRT) Paradigmas MDD symptomspezifische Prädiktoren zu ermitteln.

Methoden: Wir implementierten einen symptombasierten Ansatz, indem wir eine Drei-Faktoren-Lösung des Beck Depression Inventory (BDI) in einer Stichprobe von 47 MDD-Patienten 24 h prä und post einer einzelnen Ketamin Infusion anwendeten. Anschließend wurde die funktionelle Aktivität zu Studienbeginn im Zusammenhang mit MDD Symptomverbesserungen 24 h nach der Behandlung in einer Teilstichprobe von 16 Patienten untersucht. Weil funktionelle Abweichungen im Default Mode Network (DMN), sowie im Dorsolateralen Präfrontalen Cortex (DLPFC) mit dysfunktionalen Kognitions-Emotions Interaktionen in der Depression assoziiert werden, lag der Fokus unserer Untersuchungen auf diesen Regionen.

Ergebnisse: Auf der Verhaltensebene deuten unsere Ergebnisse darauf hin, dass Ketamin MDD-Symptome in unterschiedlichem Ausmaß beeinflusst, wobei es hauptsächlich den kognitiven Bereich betrifft.
Auf neuronaler Ebene fanden wir Hinweise darauf, dass eine verringerte DMN Deaktivierung und eine erhöhte DLPFC Aktivierung die verstärkte Wirkung von Ketamin auf kognitive Symptome prädiziert.

Schlussfolgerung: Zusammengenommen lassen diese Ergebnisse darauf schliessen, dass die antidepressive Wirkung von Ketamin durch einen „prokognitiven Mechanismus“ getrieben wird, der durch eine erhöhte Fähigkeit zur „adaptiven Anpassung“ in den beschriebenen funktionellen Netzwerken zustande kommen könnte.

Ketamine Specifically Reduces Cognitive Symptoms in Depressed Patients: An Investigation of Associated Neural Activation Patterns

3. Introduction

As one in six adults experiences Major depressive disorder at least once in their lifetime, this mental disorder is classified as one of the most widespread public health concerns (Friedrich, 2017). Furthermore, with focus on 'years lived with disability' it is the second leading contributor to global disease burden (Otte et al., 2016). With an average worldwide increase of 49.86% between 1990 and 2017, depression rates are surging significantly in most countries (Liu et al., 2020). Furthermore, depression is linked to other comorbidities such as cardiovascular diseases posing additional financial and health consequences (Seligman and Nemeroff, 2015).
Depression associated impairments result in poor psychosocial functioning and an increased risk for suicide that is almost 20 fold higher than of the average population (Chesney et al., 2014).

Risk factors for depression include stressful life events, demographic factors such as gender and age but also personality traits such as neuroticism (Kendler et al., 2005). Nevertheless, it has been found that risk factors for depression differ markedly for distinct symptoms (Lux and Kendler, 2010).

Core symptoms of MDD as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) are depressed mood, anhedonia, increased or decreased appetite, insomnia or hypersomnia, psychomotor agitation or retardation and decreased ability to think or concentrate (APA, 2013). As a substantial proportion of the involved symptoms include additional bidirectional sub-symptoms such as increase or decrease, MDD exhibits a large symptom heterogeneity that has even called into question if the disorder deserves the status of a "consistent syndrome". Consequently, two patients who receive an MDD diagnosis do not necessarily have a single symptom in common (Fried and Nesse, 2015a). This aggravates the identification of appropriate treatment strategies for the individual patient.

Antidepressant treatment approaches are still primarily based on “trial and error” and often result in symptom improvements, but not in complete remission. Unfortunately, there is very little evidence-based reliable clinical practice for choosing the “right” treatment (Voegeli et al., 2017). Treatment guidelines recommend that an initial antidepressant treatment is given for at least 4 to 6 weeks to determine a patient's response. 30% of MDD patients do not respond adequately even after multiple treatment attempts, which represents a frequent and difficult challenge for psychiatric institutions (Bauer et al., 2013). Furthermore, this complex phenomenon dramatically increases the suffering of those affected, with each failed treatment attempt. Problematically, treatment failures do not only contribute to an increase of disease burden but are also related to an enhanced risk for suicide (Reutfors et al., 2019). It is also known that each MDD episode increases the likelihood that the patient will suffer from a further depressive episode (Solomon et al., 2000).

For these reasons, it is of great importance for clinical research to develop a deeper understanding of the dynamics of different antidepressant treatments. To date, little research has been conducted about the effects of antidepressants on symptom subdimensions. This type of approach provides an opportunity to examine factors associated with treatment response that may be related to specific symptom groups and therefore more likely to be successful for a particular subset of patients.

In addition, the identification of predictive biomarkers for treatment response could be a key contributor to individualized treatment strategies. Functional neuroimaging may allow for the identification of biomarkers suited for assessing the response to a specific antidepressant treatment. If symptom subdimensions are included in the analyses, biomarkers could provide information not only on treatment success but also on the suitability for different patient groups with regard to symptomatology.

3.1 Ketamine's antidepressant efficacy

Originally known as an anesthetic, the N-methyl-D-aspartate glutamate receptor (NMDA-R) antagonist ketamine has proven to be an effective treatment for major depressive disorder (MDD). It generally shows rapid effects and high response rates, even in patients who otherwise do not respond to standard treatments. Ketamine exerts its antidepressant effects through its glutamatergic mechanism of action, which distinguishes it from most established treatments. Standard antidepressants such as SSRIs, SNRIs, TCAs, and MAO inhibitors usually exert their effects through the aminergic system and often have a delayed onset of action with several weeks to months to reach their full potential (Hillhouse and Porter, 2015).

For this reason, more rapid acting therapeutic agents, with antidepressant effects occurring within hours or days, are urgently needed. Antidepressant pharmacotherapies that primarily target the glutamatergic system are thought to provide more rapid therapeutic benefits. Subanesthetic doses of ketamine have been shown to produce fast antidepressant effects within 24 hours of a single intravenous infusion in up to 50% of patients who are otherwise considered treatment-resistant (Ionescu et al., 2018). The effect targets various MDD symptoms and is usually stable for up to one week (Shin and Kim, 2020). All of this makes ketamine a valuable research tool to develop the next generation of fast-acting antidepressants. Nevertheless, its symptom specificity and precise neurobiological mechanisms remain unclear (Shin and Kim, 2020). Thus, a better understanding of the mechanisms associated with these rapid antidepressant effects and the identification of symptom-specific biomarkers of treatment response contribute substantially to clinical research.

3.2 Symptom dimensions of major depressive disorder

Distinct MDD symptoms differ in fundamental aspects such as associated biological factors, the impact on functional impairments, or the underlying risk factors. Furthermore, a marked heterogeneity exists with regard to the distribution of symptom profiles. This implies that the use of sum scores as an estimate of depression severity may not be appropriate. They may provide an estimate of overall psychopathological load, wherein it needs to be incorporated that different symptom profiles carry differential impairment in psychosocial functioning (Fried et al., 2014) (Fried and Nesse, 2014; Tweed, 1993). This means that individuals with similar sum scores may have very different syndromes, and that depression can be very severe even when only a few symptoms are present (Fried and Nesse, 2015a)

The predominant use of sum scores in depression research has even been suspected as a major reason why there has been scarcely any progress in characterizing new antidepressant therapeutics or effective biomarkers (Fried and Nesse, 2015b). Observations on many levels of research suggest that the analysis of symptom dimensions is of increased efficiency in MDD research. For instance, against the majority of common hypothesis, a recent endocrinological study indicated that less than half of diagnosed MDD patients show increased levels of inflammation (Raison and Miller, 2011), whereby somatic symptoms such as problems with appetite or sleep were shown as significantly linked to inflammatory markers (Duivis et al., 2013). These observations suggest a symptom specificity that would remain unrevealed by the use of standard sum score analyses.

Risk factor studies based on sum scores have indicated that female medical residents have a greater tendency to develop depression. In contrast, analysis of individual symptoms reveal that male medical residents under stress have increased suicidal ideation, while female study participants were more likely to develop difficulties to concentrate or problems with appetite or sleep (Fried et al., 2014). An examination of disturbed emotion regulation strategies as risk factors for MDD has shown that frequent repetitive negative thinking and infrequent positive reappraisal are associated differentially with affective, cognitive, and somatic symptoms (Everaert and Joormann, 2019). Moreover, genetic research has implied that depressive symptoms are associated, to varying degrees, with specific genetic polymorphisms (Myung et al., 2012).
Taken together, these studies provide evidence that symptom-level approaches involving MDD subdimensions might help to gain a more sophisticated understanding on the mechanisms of depression and on how they are affected by different psychotherapeutic treatments.

In this context, the Beck Depression Inventory-II (BDI-II) in combination with Osman's factor structure model appear as a promising design striving after the exploration of MDD symptom specific treatment response (Osman et al., 1997; Wang et al., 2013). The BDI as one of the most prevalent patient-rated measures of depression severity assesses a large number of aspects of depressive symptomatology (i.e. 21 items) with high reliability (Cusin et al., 2010). The three-dimensional factor model of Osman has demonstrated good fit for clinical samples and was evidenced as one of the best suited instruments for the investigation of depressive symptom dimensions. It offers the rare advantage of unidimensionality, referring to the fact that each BDI item loads onto a single subdimension (i.e. cognitive, affective or somatic) (Osman et al., 1997; Vanheule et al., 2008). This type of approach allows for a more finetuned measurement of symptom dimensions and may have greater utility in understanding the mechanisms of MDD and pathophysiologic biomarkers, which could contribute to increased efficacy of existing treatment interventions.

3.3 Ketamine's impact on cognitive outcome in MDD

Two-thirds of MDD patients experience cognitive dysfunctions, which often persist after other MDD symptoms have resolved (Semkovska et al., 2019). In addition, depression research has implicated that cognitive impairment is associated with disturbed emotion regulation and, thus, poses an increased risk for treatment resistance or even suicide (Averill et al., 2016).

Furthermore, disrupted cognition-emotion interaction is thought to result in working memory (WM) deficits referring to the ability to maintain or manipulate information over a short period of time. As these processes are required in all day-to-day activities, their impairments crucially reduce quality of life and functional capacity (LeMoult and Gotlib, 2019). It has previously been suggested that the antisuicidal effect of ketamine is primarily due to its influence on the cognitive domain and related brain networks (Lee et al., 2016). Other studies have supported this hypothesis by observing how cognitive impairment decreased in a group of bipolar patients after a single ketamine administration (Permoda-Osip et al., 2015) and likewise after multiple administrations in unipolar depressed patients (Basso et al., 2020).

Accumulating evidence implies a neurocognitive predictor of ketamine response, as poor neurocognitive performance prior to treatment was associated with successful therapy (Shiroma et al., 2014). Moreover, immediate decrease in cognitive performance post-administration predicted subsequently reduced response rates (Murrough et al., 2013).

On a neurobiological level, NMDA-Rs are known to play an important role regarding the interaction between cognition and emotion, whereby ketamine as an NMDA-Rs antagonist is considered to positively influence WM through its impact on this interaction (Scheidegger et al., 2016a). Its beneficial effect on cognitive functioning has been considered to originate from increased prefrontal control resulting from large scale network configurations (Gärtner et al., 2019).

3.4 fMRI during WM or emotional stimulation

At the level of activity and connectivity, neuroimaging research is providing increasingly deep insights into the interplay of different brain structures at different stages of information processing, from encoding all the way to retrieval (LaBar and Cabeza, 2006). During these processes, our complex dynamic behavior is controlled by reciprocal influences between emotion and cognition. Areas in the prefrontal cortex for instance are considered to be mainly responsible for cognitive processes, whereas areas in the limbic system such as the amygdala are regarded as preliminary involved in affective processes (Dolcos et al., 2011). Meanwhile, converging evidence suggests that cognition and emotion, which have previously been considered as located in separate neural systems, appear to be integrated in networks that exhibit a high degree of connectivity and interaction (Pessoa, 2008). The lateral prefrontal cortex is one example of a brain region in which cognition and emotion are conjointly integrated. This was demonstrated in a study in which participants were asked to solve a working memory task after watching short, emotionally challenging videos, whereupon activity in this region reflected both emotional and working memory components (Gray et al., 2002).

The n-back task is a widely used working memory paradigm in which participants must decide whether a currently presented stimulus matches the one shown n trials earlier. This is intended to trigger numerous processes regarding working memory including monitoring, updating, and manipulating previously remembered information (Owen et al., 2005). When studying WM associated emotion stimulation, a major challenge is to elicit emotions in a controlled manner. Herein, a common method is to use emotionally valenced words to study how emotional stimuli affect activity in the brain (Grimm et al., 2012). After stimulus presentation, brain reactivity is measured and responses to emotionally valenced stimuli are compared to neutral control material. In contrast, WM reactivity is measured by comparing brain activation during positive, negative, or neutral stimuli with those during a fixation condition.

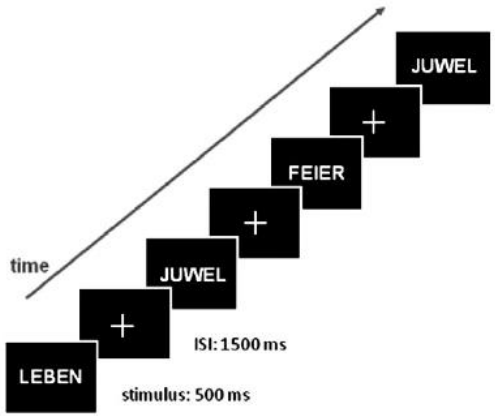

Figure 1: Illustration of the n-back task paradigm conducted during fMRI measurement. Positive, negative or neutral valenced word stimuli are presented for 500 ms with an interstimulus interval (ISI) of 1500 ms, each followed by a fixation trial (10–14 s).

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Negative mood has been shown to reduce performance in working memory tasks (Aoki et al., 2011). In addition, MDD is known to be frequently associated with profound working memory dysfunctions, which can be observed in related brain regions (Gärtner et al., 2018). Overall, psychiatric research is starting to recognize that most psychiatric disorders are not only marked by alterations in emotional processing, but also by cognitive disturbances (Millan et al., 2012). On these grounds, in depression research we consider the analysis of prediction of therapeutic responses during WM or emotional stimulation as more promising than during the resting state, because those brain areas are engaged which play a role in mental disorders.

3.5 Neural activation patterns associated with major depressive disorder

Various alterations in regional brain functions have been associated with MDD, whereby no distinct functional aberration can explain all aspects of the disease. Nevertheless, particular functional networks have been repeatedly associated with depression and the disturbed interaction of cognition and emotions: the default mode network (DMN) (Zhou et al., 2020) as well as the cognitive and the affective control network (Wang et al., 2016).

The DMN consists of a subset of brain areas including the pregenual anterior cingulate cortex (pgACC), the posterior cingulate cortex (PCC) and the dorsomedial prefrontal cortex (DMPFC). They exhibit functional activity correlations when a person is engaged in self-referential processing such as thinking about the self or others, reflecting about the past or contemplating about the future. During the performance of emotional-cognitive tasks demanding external focus, healthy subjects typically exhibit suppressed DMN activity (Buckner et al., 2008; Fox and Raichle, 2007). Contrarily, MDD patients show a lack of deactivation during externally focused tasks next to an increased activation during rest (LeMoult and Gotlib, 2019). This is supposed to result in cognitive risk factors for depression such as rumination and emotion related cognitive biases in terms of mood congruent interpretation, working memory and attention (Grimm et al., 2011, 2009; Korgaonkar et al., 2013; Nixon et al., 2013; Sheline et al., 2009).
The DMPFC has been described as potential predictor for antidepressant treatment response. Its WM-related activation was linked to treatment induced amelioration of MDD symptoms and recovery from WM deficits (Meyer et al., 2019). Moreover, DMPFC activation during negative emotion perception was associated with treatment success in pharmacological responders (Samson et al., 2011).

The cognitive control network (CCN) consists of lateral-prefrontal and parietal brain regions and includes the DLPFC. It plays a central role in the top down control of emotions and in suppressing task-irrelevant information. The cognitive control network is typically under-engaged in MDD which is thought to result in poor concentration, disrupted cognitive processing, reduced inhibition of irrelevant negative stimuli and poor ability to generate novel strategies (Rayner et al., 2016). Underlining research reports increased frontal task-related activation in MDD patients that do not suffer from WM impairments, which was interpreted in terms of hyperfrontality as a compensating effect for impaired deactivation of the DMN (Gärtner et al., 2018).

The affective network (AN) mainly consists of limbic structures such as hippocampus, amygdala and subgenual anterior cingulate cortex (sgACC) and is responsible for emotional processing and the mediation of mood states. Neuroimaging evidence has indicated that missbalanced prefrontal-limbic neuronal activation is linked to aberrant cognition-emotion interaction (Gärtner et al., 2018; Rayner et al., 2016).

Overall, the dysfunctional interaction between the circumscribed neural networks is supposed to be closely linked to MDD pathology influencing various features of the disease. Accordingly, it was shown that during an emotional-cognitive task, MDD patients show elevated DLPFC activation and reduced deactivation in DMN regions (Gärtner et al., 2018; LeMoult and Gotlib, 2019). In this context, prior studies show that WM-related activity in these regions differs significantly between MDD patients and healthy controls. A multivoxel pattern classification approach further indicated that healthy controls and MDD patients can be distinguished with a high degree of accuracy (Gärtner et al., 2018).

3.6 Neural activation patterns associated with ketamine's antidepressant efficacy

Evidence from a functional connectivity study indicates that the dorsal nexus as an interconnecting brain hub between DMN and limbic-prefrontal regions demonstrates ketamine induced connectivity reductions to the aforementioned brain areas (Scheidegger et al., 2012). Further, ketamine is supposed to disrupt depression related hyperconnectivity within prefrontal and subcortical networks involved in the ability to switch from an internal self-referential to an external goal-oriented mode (Ionescu et al., 2018).

A previous neuroimaging study involving an emotional WM task demonstrated that ketamine reduces negative emotional interference with cognitive processing mechanisms. It was stated that ketamine's beneficial effect on MDD might result from restoration of functional interactions between regions of cognitive control and the DMN (Scheidegger et al., 2012). Accordingly, during emotional as well as attentional processing, MDD patients have demonstrated activity normalization in fronto-parietal regions following ketamine administration (Reed et al., 2019, 2018). Additionally, ketamine was shown to attenuate emotion-related activation in the AN (Scheidegger et al., 2016b).

Altogether, the normalization of brain activation in these areas is regarded as crucial to ketamine's antidepressant efficacy. However, the majority of neuroimaging studies striving to uncover the related mechanisms has been compiled during rest in samples of healthy participants, which allows no direct conclusion about the association of WM related activation with the antidepressant effect. The rare amount of existing task-based ketamine studies have mostly focused on emotion stimulation rather than emotional WM tasks (Ionescu et al., 2018). As functional aberrations in emotion-cognition related brain areas have been described as potential predictors for successful ketamine treatment, we consider the investigation of their WM related BOLD reactivity as a promising strategy concerning the exploration of symptom specific treatment response in MDD (Grimm et al., 2012).

4. Material and Methods[a]

4.1 Subjects

A total sample of 47 male and female patients diagnosed with MDD according to DSM 5 criteria (mean age 47.15 ± 12.58 years (SD); 23 males and 24 females) were recruited at the Department of Psychiatry, Psychotherapy and Psychosomatics, University of Zurich (UZH, n = 14) and the Department of Psychiatry, Charité Universitätsmedizin Berlin (CHAR, n = 33). A subsample of 16 patients (mean age 44.19 ± 14.92 years (*SD*); 6 males and 10 females) underwent fMRI scanning (see Table 1). General exclusion criteria were: Cardiovascular diseases, recent heart or head surgery, current pregnancy, relevant psychiatric or neurological diseases in particular dementia, epileptic seizures, schizophrenia, psychosis, or acute suicidality, presence or history of substance abuse or dependence, and treatment with electroconvulsive therapy in the previous six months. We included patients currently taking psychopharmacological medication in terms of monotherapy, augmentation, or adjunctive therapies in the study. Current medication intake was documented as shown in the results section. For the fMRI subsample additional MR standard exclusion criteria were applied. The study was conducted according to the latest version of the Declaration of Helsinki. The full procedure and purpose of the study were explained to each subject in detail as approved by the institutional review boards and Ethics Committee of the CHAR and UZH before they gave written informed consent (Stippl et al., 2021).

[a] Adapted with permission from my previously published original article, in which I am the sole first author: Stippl, A., Scheidegger, M., Aust, S., Herrera, A., Bajbouj, M., Gärtner, M., Grimm, S., 2021. Ketamine specifically Reduces cognitive symptoms in depressed patients: An investigation of associated Neural activation patterns. *Journal of Psychiatric Research* 136, 402–408.https://doi.org/10.1016/j.jpsychires. 2021.02.028
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Table 1.

Demographic, clinical, and behavioral data at baseline

	Total sample (N=47)	FMRI subsample (N=16)
Age (M,SD)	47.15 ± 12.58	44.19 ± 14.92
Sex (m/f)	24/23	6/10
BDI (M,SD)	32.43 ± 10.76	30.19 ± 11.51
MADRS[a] (M,SD)	25.64 ± 5.93	26.00 ± 6.34
Intake of antidepressants[b]	32 (of n=43)[c]	15
SSRI's	11 (of n=43)[c]	6
SSNRI's	13 (of n=43)[c]	8
Tricyclics	10 (of n=43)[c]	2
Anticonvulsants	9 (of n=43)[c]	4
Benzodiazepines	8 (of n=43)[c]	5
Neuroleptics	14 (of n=43)[c]	6
Number of depressive episodes	5.19 ± 4.11 (of n=27)[c]	-
Duration of current episode in months	29.37 ± 19.77 (of n=27)[c]	-

BDI Beck Depression Inventory, MADRS Montgomery Asberg Depression Rating Scale, [a] Summarized MADRS scores for subjects at CHAR and converted HAMD scores for subjects at UZH, [b] Number of patients taking antidepressants during the study, [c] Proportion of the overall sample with complete information on the subject, SSRI's Selective serotonin reuptake inhibitors, SSNRI's Selective noradrenaline reuptake inhibitors

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4.2 Experimental design

Following a naturalistic clinical study design, all subjects received a single dose of ketamine intraveneously over 40 min administered by psychiatrists and anaesthesiologists of the respective clinic. Subjects from UZH received 0.25 mg/kg S-ketamine (Ketanest® S, Pfizer, Zurich, Switzerland) and subjects from Berlin received 0.5 mg/kg racemic ketamine (R/S, enantiomer ratio of 1:1). Because S-ketamine exerts a 3–4 times higher potency or receptor affinity than racemic ketamine, doses are typically reduced by 50% (Hashimoto, 2019; Sinner and Graf, 2008).

For clinician-rated assessment of depression severity at baseline, the Montgomery Asberg Depression Rating Scale was used at CHAR (MADRS; Montgomery and Asberg, 1979) and the Hamilton Depression Rating Scale at UZH (HAM-D; Hamilton, 1980). For symptom self-assessment 24 h pre- and post-intervention each participant completed the Beck Depression Inventory (BDI). The 24h follow-up time point for the BDI assessment was based on the observation that ketamine's antidepressant effect is most pronounced one day post administration (Zarate et al., 2006). All subjects in the subsample additionally completed a task-related fMRI session, 24 h prior to a single sub-anesthetic dose of ketamine (Stippl et al., 2021).

4.3 Self-rated depression severity

In order to examine whether a single ketamine infusion differentially affects depressive symptom dimensions (cognitive, affective, somatic) measured by the BDI, we applied a three-factor solution (Osman et al., 1997; Buckley et al., 2001). Accordingly, each of the 21 BDI items was ascribed to one of the symptom dimensions and the respective scores were calculated. To acquire a measure for the change in symptom dimensions, a Percent Change to Baseline (PCB) response value was calculated for each subject between pre- and post-intervention with the following formula: ((baseline - follow-up) / baseline) * 100 (Stippl et al., 2021).

4.4 Working memory task

During fMRI measurements, subjects performed an emotional n-back task using verbal stimuli selected from the Berlin Affective Word List (BAWL (Võ et al., 2009)). In concordance with the BAWL norms, stimuli were categorized as positive, negative or neutral and matched according to the number of letters, imageability, frequency of

appearance and emotional arousal level. Stimuli were presented in 15 blocks, 5 of each valence category (positive, negative or neutral) separated by fixation trials of 10–14 s. Each block contained 15 words presented for 500ms with
an interstimulus interval of 1500 ms. Subjects were required to monitor a series of words and to respond whenever a word was presented that was the same as the one presented 2 trials previously. This task has been proven to elicit blood oxygenation level-dependent (BOLD) responses in emotion and WM related brain regions (Grimm et al., 2012; Scheidegger et al., 2016a). Stimuli were generated by Presentation® (Neurobehavioral Systems, Inc., Albany, CA, USA) and presented via video goggles (VisuaStim digital, Resonance Technology, Inc., Los Angeles, CA, USA). Participants responded by pushing a fiber-optic light sensitive key press. WM performance was assessed by calculating an accuracy score (hits – false alarms / target * 100) and reaction times to the stimuli (Stippl et al., 2021).

4.5 fMRI data acquisition and analysis

Functional magnetic resonance imaging data was acquired on a Philips Achieva 3T scanner (UZH), and a Siemens Trio 3T (CHAR) applying standard echo planar imaging sequences (Grimm et al., 2012; Scheidegger et al., 2016). In short, functional images were recorded in runs of 10 min with 331 volumes. At UZH sequence parameters were set to 32 contiguous axial slices of 4 mm (TE = 35 ms; field of view = 22 cm; voxel size = 2.75 x 2.75 x 4 mm, TR 3000 ms, flip angle 82°). Sequence parameters at CHAR were set to 37 oblique axial slices of 3 mm (TE = 30 ms; field of view = 192 mm, voxel size 3×3x3 mm, TR 2000 ms, flip angle 70°). FMRI data were analyzed using MATLAB 2012b (The Mathworks Inc.,Natick, MA, USA) and SPM12 (Statistical parametric mapping software, SPM; Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk). Functional images were realigned according to the first volume and corrected for motion artifacts. Normalization was adjusted to a standard stereotactic space template from the Montreal Neurological Institute (MNI) and spatial Smoothing was processed using a 6 mm FWHM Gaussian kernel. The time series were high-pass filtered to eliminate low-frequency components (filter width 128 s) and adjusted for systematic differences across trials. Statistical analysis on the subject level was performed by modeling the different conditions convolved with a hemodynamic response function as explanatory variables within the context of the general linear model on a voxel-by-voxel basis. Realignment parameters were included as additional regressors in the statistical model. A fixed-effect model was performed to create images of parameter

estimates, which were then entered into a second-level random-effects analysis. For each subject, the following contrast images of parameter estimates were calculated: 1. All WM conditions versus fixation condition (WM>Fixation); 2. Emotional WM conditions versus neutral WM condition (Emo>Neutral).

Regions-of-interest (ROIs) were defined to examine WM related brain activations at baseline. Specifically, the following ROIs that have been previously linked to WM (dys-)function and aberrant emotional processing in depression were selected (abbreviation and MNI coordinates in brackets): the bilateral dorsolateral prefrontal cortex (lDLPFC; ±40 36 32), the posterior cingulate cortex (PCC; 0 -48 26); dorsomedial prefrontal cortex (DMPFC; 0 52 36), the bilateral amygdala (±24 -2 -20) , the bilateral anterior Insula (±34 20 0) and the pregenual anterior cingulate cortex (pgACC; 0 42 2) (see Fig.2). Spherical ROI templates were built with automated term-based meta-analyses on neurosynth.org and our own previous work. The mean activity level of each was extracted using the REX Toolbox (https://www.nitrc.org/projects/rex/) (Stippl et al., 2021).

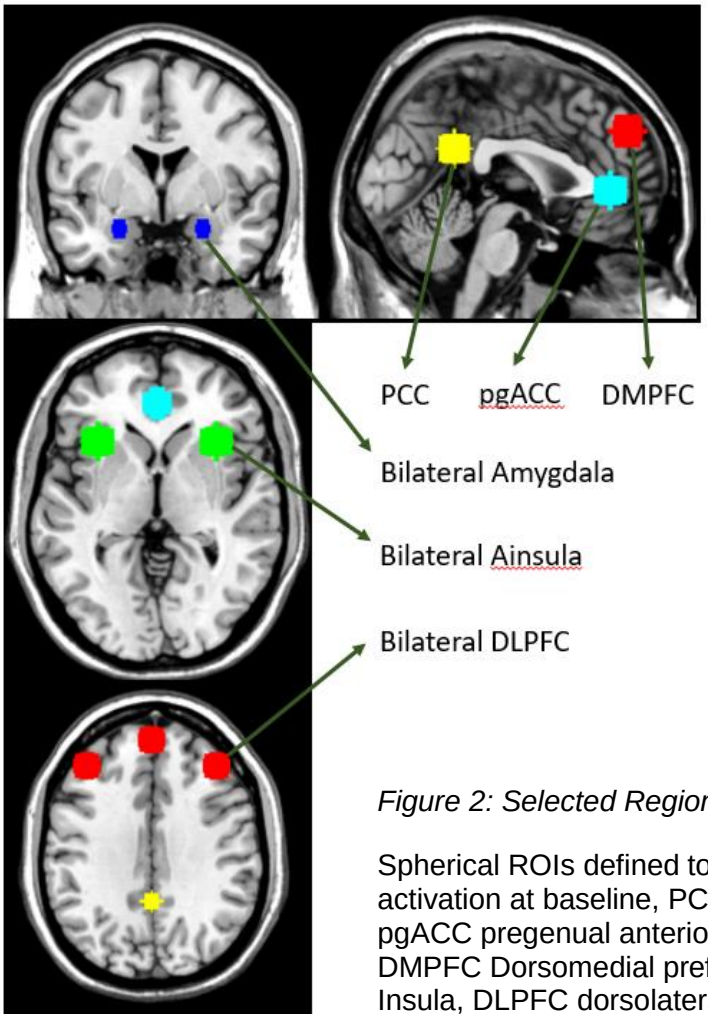

Figure 2: Selected Regions-of-interest (ROIs) spheres

Spherical ROIs defined to examine WM related brain activation at baseline, PCC posterior cingulate cortex, pgACC pregenual anterior cingulate cortex, DMPFC Dorsomedial prefrontal cortex, AInsula anterior Insula, DLPFC dorsolateral prefrontal cortex.

4.6 Statistical group analysis

For the analysis of ketamine effects on BDI subdimensions a one-way ANCOVA with the 3-level factor *BDI dimension* (cognitive, affective, somatic) was calculated. Planned paired post hoc comparisons were calculated in case of a significant main effect. To rule out biasing effects of overall depression severity, the total BDI score at baseline was entered as a covariate.

The main fMRI group analysis was conducted on average brain activations in predefined ROIs. WM related baseline activity in these ROIs was correlated with the percentage of symptom reduction after ketamine using Pearson's correlation coefficient. Bonferroni correction was applied to correct for multiple testing. Uncorrected results are reported as exploratory findings. Statistical analyses on clinical and ROI data were carried out using PASW (Predictive Analysis SoftWare, version 25.0, Chicago: SPSS Inc., Illinois, USA). Additionally, a multiple regression model was applied on the whole-brain level to identify clusters of activation correlating with symptom reduction. Statistical thresholds were set to $p < 0.001$ (uncorrected) at the single voxel level and to $p < 0.05$ (FDR corrected) at the cluster level. However, because of the small sample size, uncorrected results are reported and marked as exploratory findings. The statistical whole brain group analyses were conducted in SPM (Stippl et al., 2021).

5. Results[b]

5.1 Clinical results

On average, patients had a total BDI score of 32.43 (SD 10.76) at baseline. HAMD scores of subjects at UZH were converted into MADRS scores to fit rating scales of subjects at CHAR (Leucht et al., 2018). On this basis an overall depression score of 25.64 (SD 5.93) was calculated at baseline. Twenty-four hours after ketamine administration, the average total BDI score was 24.55 (11.57). The average symptom reduction after ketamine was 21.97 (SD 27.9) %. Cognitive symptoms were reduced by 27.53 (SD 34.89) % after ketamine, affective symptoms by 19.8 (SD 40.11) %, and somatic symptoms by 15.81 (33.42) % (see Table 2 and Fig.3). The ANCOVA calculated for differences in symptom reduction between BDI dimensions revealed a significant main effect ($F(2,45) = 3.28$, $p = 0.042$). Paired comparisons showed that cognitive symptoms were stronger reduced than somatic symptoms ($p = 0.01$). No difference was observed for the other post hoc comparisons. On a descriptive level the strongest symptom reduction was observed for the cognitive dimension (see Fig.3) (Stippl et al., 2021).

[b] Adapted with permission from Stippl, A., Scheidegger, M., Aust, S., Herrera, A., Bajbouj, M., Gärtner, M., Grimm, S., 2021. Ketamine Specifically Reduces cognitive symptoms in depressed patients: An investigation of associated neural Activation patterns. *Journal of Psychiatric Research* 136, 402–408.https://doi.org/10.1016/j.jpsychires.2021.02.028. All referenced tables and figures appear in the original paper. According to Elsevier´s published guidelines on using copyrighted work an author can, include the article in full or in part in a thesis or dissertation.

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Table 2.

Clinical data for BDI overall symptom score or subdimensions.

Total BDI score and values of cognitive, affective and somatic BDI subdimensions at baseline, 24 h post- a single sub-anesthetic ketamine infusion, and resulting Percent Change to Baseline values (N=47).

	Baseline	post 24 hrs.	PCB (%)	P-value
BDI total (M,SD)	32.43 (10.76)	24.55 (11.57)	21.97 (27.90)	< 0.001
BDI cognitive (M,SD)	11.06 (4.89)	8.00 (5.20)	27.53 (34.89)	< 0.001
BDI affective (M,SD)	7.85 (2.64)	5.98 (3.12)	19.80 (40.11)	< 0.001
BDI somatic (M,SD)	12.04 (4.21)	9.51 (4.36)	15.81 (33.42)	< 0.001

BDI Beck Depression inventory, M Mean, SD Standard Deviation, PCB Percent Change to Baseline

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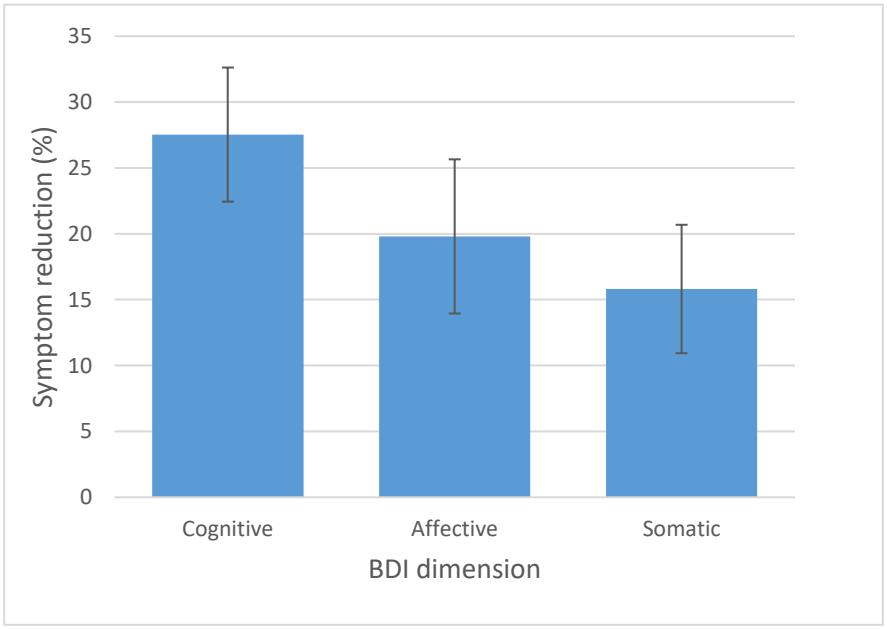

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Figure 3: Symptom reduction in BDI subdimensions (Mean ± SEM)

Percent Change to Baseline in cognitive, affective and somatic symptom subdimensions of the BDI 24 h between pre- and post- a single sub-anesthetic ketamine infusion (N=47).

Table 3.

Responders for total BDI score and symptom subdimensions.

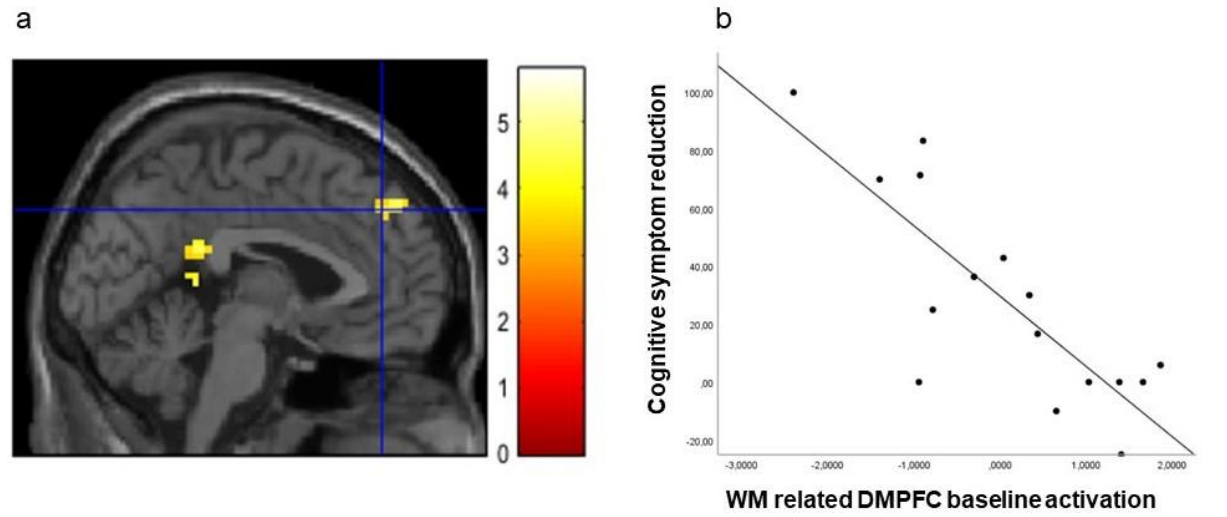
Number of responders and partial responders regarding the Percent Change to Baseline values 24 h pre- and post- ketamine infusion for the total BDI score and for cognitive, affective and somatic BDI subdimensions (N=47).

	% Mean PCB (SD)	Responder (n)	Partial Responder (n)
BDI total (M,SD)	21.97 (27.90)	8	17
BDI cognitive (M,SD)	27.53 (34.89)	13	22
BDI affective (M,SD)	19.80 (40.11)	11	19
BDI somatic (M,SD)	15.81 (33.42)	10	19

BDI Beck Depression inventory, SD Standard Deviation, M Mean, Responders defined as 50% reduction of symptoms, Partial Responders defined as 25% reduction of symptoms

5.2 fMRI results

The ROI analysis showed a highly significant association between WM-related baseline activity in the DMPFC and the reduction of cognitive symptoms after ketamine ($r(14) = -0.72$, $p = 0.0018$; see Fig.4). Additional uncorrected results are shown in Table 4 (Stippl et al., 2021).



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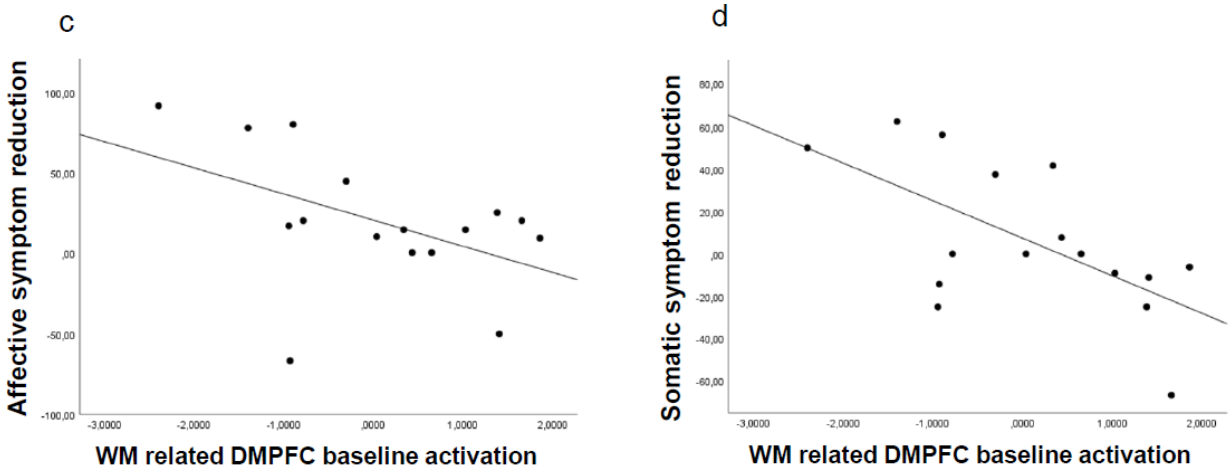

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Figure 4: WM related DMPFC BOLD reactivity at baseline correlates negatively with cognitive symptom change 24h after ketamine infusion

a) Whole Brain DMPFC cluster with peak activation at [6, 38, 40] related to cognitive symptom change. **b)** Visualization of association between WM related single subject activation in marked whole brain DMPFC cluster at baseline and **cognitive** symptom reduction after ketamine. Abbreviations: WM working memory, DMPFC dorsomedial prefrontal cortex, BOLD blood oxygen level dependent. **c)** Association between WM related single subject activation in marked whole brain DMPFC cluster at baseline and **affective** symptom reduction after ketamine **d)** Association between WM related single subject activation in marked whole brain DMPFC cluster at baseline and **somatic** symptom reduction after ketamine

Table 4.

ROI results for WM related brain activations linked to symptom reduction

ROI	Cognitive		Affective		Somatic	
	r	**p**	**r**	**p**	**r**	**p**
DMPFC	-0.72	0.0018*	-0.49	-	-0.46	-
PCC	-0.61	0.013	-0.18	-	-0.13	-
Left AInsula	-0.45	-	-0.62	0.01	-0.29	-
Left AM	-0.5	0.049	-0.52	0.038	-0.44	-
Left DLPFC	0.51	0.043	0.14	-	0.11	-
pgACC	-0.33	-	-0.44	-	-0.1	-
Right AInsula	-0.24	-	-0.33	-	-0.31	-
Right AM	-0.3	-	-0.24	-	-0.21	-
Right DLPFC	0.47	-	0.23	-	0.3	-

Notes. * corresponding p-value of p<=0.05 (uncorr), DMPFC dorsomedial prefrontal cortex, PCC posterior cingulate cortex, AInsula anterior Insula, AM amygdala, DLPFC dorsolateral prefrontal cortex, pgACC pregenual anterior cingulate cortex

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The analysis of associations between emotion processing during the WM task and symptom reduction revealed no significant Bonferroni corrected correlations. On an uncorrected level there were two positive correlations between symptom reduction in the cognitive dimension and the right amygdala (r = 0.53, p = 0.03), and the pgACC (r = 0.64; p= 0.008), respectively (see Fig.5). No correlations were observed for the other two dimensions (Stippl et al., 2021).

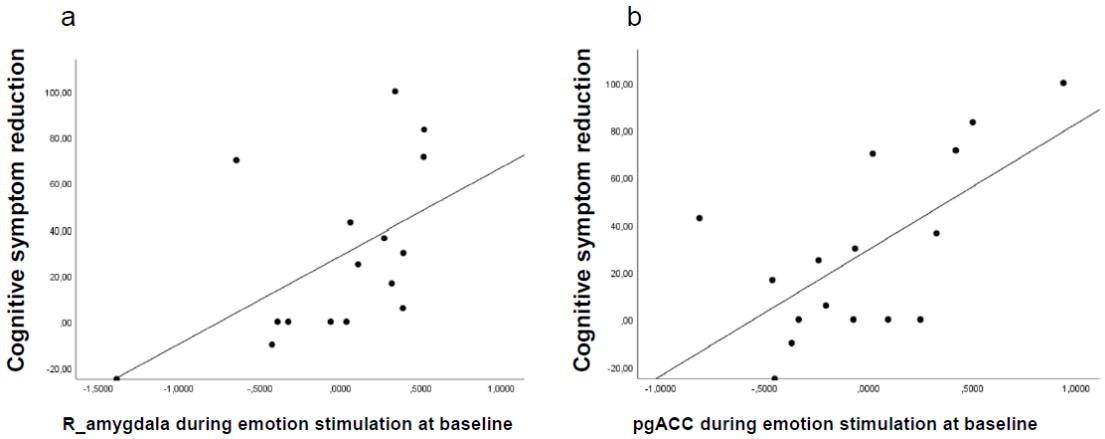

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Figure 5: DMPFC BOLD reactivity during emotion processing at baseline correlates positively with cognitive symptom change 24h after ketamine infusion

a) Uncorrected results for activation in right amygdala ROI sphere of 5 mm [24 -2 -20] during emotion processing related to cognitive symptom change. **b)** Uncorrected results for activation in pregenual anterior cingulate cortex ROI sphere of 5 mm [0 42 2] during emotion processing related to cognitive symptom change.

The whole-brain fMRI analysis showed no significant results after FDR correction on the cluster level. However, exploratory analysis (cluster alpha < 0.05, uncorrected) revealed several brain areas associated with symptom reduction in distinct BDI dimensions. Only negative associations were observed, with lower levels of baseline activation corresponding to higher levels of symptom reduction 24 hours after ketamine (Table 5) (Stippl et al., 2021).

Table 5:

Whole-brain results for WM related brain activations linked to symptom reduction in cognitive, affective and somatic BDI subdimensions

BDI dim	Cluster	K-Size	p (unc.)	x	y	z
cognitive	left Amygdala	14	0.026	-27	-4	-26
cognitive	left VMPFC	17	0.016	-30	41	22
cognitive	right PostCG	11	0.045	45	-25	34
cognitive	DMPFC	14	0.026	6	38	40
cognitive	PCC	12	0.037	0	-40	22
cognitive	PCC	18	0.013	3	-46	10
affective	DMPFC	19	0.012	-3	14	64
affective	left Insula	11	0.046	-33	5	-5
somatic	right ITG	31	0.002	54	-49	-8
somatic	right PostCG	27	0.003	42	-25	40
somatic	ACC	13	0.031	-6	20	31
somatic	left PreCG	16	0.018	-51	-13	34
somatic	left IPL	11	0.045	-36	-34	40

BDI dim Beck Depression Inventory dimension, VMPFC ventromedial prefrontal cortex, PostCG postcentral gyrus, DMPFC dorsomedial prefrontal cortex, PCC posterior cingulate cortex, ITG inferior temporal gyrus, ACC anterior cingulate cortex, PreCG precentral gyrus, IPL inferior parietal lobule

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6. Discussion

The investigation of mechanisms underlying ketamine's attenuating effect on MDD symptomatology is hindered by the heterogeneity of depression related clinical profiles (Bauer et al., 2013; Fried and Nesse, 2015a). Due to this fact, current research indicates that models categorizing rating scale items into distinct subdimensions may have bigger benefit than established sum score analysis which allow no sensitive detection of symptom specific changes (Chekroud et al., 2017; Fried and Nesse, 2015a). To promote our understanding of depression, the diversity of underlying symptom profiles and their adequate treatment, we focused on the examination of the effects of a single sub-anesthetic ketamine infusion on distinct MDD symptom dimensions.

Aiming to identify treatment- and symptom specific response predictors, we additionally accessed WM related BOLD reactivity at baseline associated with symptom change in cognitive, affective and somatic dimensions following ketamine administration in a subgroup of patients.
Only a sparse amount of clinical neuroimaging studies has analyzed functional activation patterns as biomarkers for successful ketamine treatment and none has yet focused on the prediction of symptom specific treatment response. Functional aberrations in emotion-cognition related brain areas such as the default mode network (DMN) or prefrontal regions have been described as potential predictors for successful ketamine treatment. However, the predictive values of those brain areas regarding specific symptom improvement remain unexplored.

In line with our hypotheses, the behavioral results in this study demonstrate that ketamine affects symptoms of MDD to varying degrees, with the greatest reduction in the cognitive domain (Stippl et al., 2021). These findings corroborate a previously mentioned theory in which the acute effects of ketamine on cognition and associated neural circuitry are described as mediating factors in terms of its antidepressant efficacy (Lee et al., 2016). Other studies have been able to confirm this theory of a procognitive mechanism by observing cognitive improvements in depressive patients after single or repeated administration of ketamine (Basso et al., 2020; Chen et al., 2018; Permoda-Osip et al., 2015). Additionally, neurocognitive performance prior and right after ketamine administration has been associated with a subsequent antidepressant response, suggesting a potential neurocognitive predictor (Murrough et al., 2013; Shiroma et al., 2014) that might coincide with our observation of ketamine's effect on cognitive deficits.
However, to the best of our knowledge, our findings provide first evidence that ketamine's effect on cognitive symptoms is more pronounced than on affective or somatic symptoms. This is illustrated both with regard to improvement of cognitive, affective and somatic symptoms as measured by the BDI (see Fig.3) as well as regarding the number of responders and partial responders with respect to these symptom dimensions (see Table 3).

Here, it might be noted that the amount of responders does not vary greatly across the different dimensions, but the magnitude of the effect is substantially increased with respect to the cognitive symptoms. Furthermore, it might be remarked that the total reduction in depression severity in our study appears to be rather low compared to previous examinations, where response rates ranged from about 25% to 85% 24 hours after ketamine administration, depending on the study (Abdallah et al., 2015). The response rates of our sample are at the lower end of this range, which might be explained by the fact that typically most of our patients were recruited from clinical departments specialized in the treatment of chronic and severe affective disorders. Therefore, many of these patients are considered highly treatment-resistant and might therefore differ from the "average" MDD patient population in terms of their response rates to ketamine.

Our neuroimaging data indicated that the described marked effect of ketamine on cognitive symptoms is associated with lower WM-related DMPFC deactivation and higher DLPFC activation prior to treatment (see Table 4) (Stippl et al., 2021). The significant association of baseline DMPFC activation with cognitive symptom change 24 h after ketamine administration is illustrated in Fig.4 a. While, brain activation within the same extracted DMPFC cluster showed no significant correlation with affective or cognitive symptom change as illustrated in Fig. 4 b and c. This might be explained by the previously described fact that the DMPFC is part of the DMN, a network of brain areas exhibiting deactivation during emotional–cognitive tasks and enhanced activation during the resting state (Buckner et al., 2008; Fox and Raichle, 2007). Accumulating evidence indicates that MDD patients show disruptions in their ability to regulate activation in these areas, which results in depression related cognitive deficits (Grimm et al., 2011, 2009; Korgaonkar et al., 2013; Nixon et al., 2013; Sheline et al., 2009). Further, WM related activation patterns in DMN regions were proven as distinguishable between MDD patients and healthy controls by showing less deactivation in the depressed brain (Gärtner et al., 2018). Even in healthy subjects, malfunctioning deactivation of the DMN during external processing was shown to result in aberrant cognitive functioning (Bonnelle et al., 2011).

In contrary, the DLPFC as part of the CCN is supposed to regulate activation in regions of the DMN and thus conrol for cognition-emotion interaction (Rayner et al., 2016). MDD related interference of maladaptive emotion processing with cognitive functioning might be due to the dysfunctional interaction of these regions (Grimm et al., 2012; LeMoult and Gotlib, 2019).
On these grounds, our observation of the association between decreased pretreatment WM related DMPFC deactivation and increased DLPFC activation with post treatment cognitive improvements might indicate a generally elevated potential for the adaptive adjustment in these neurocircuits (Diener et al., 2012), which in turn predicts a more pronounced effect of ketamine on cognitive symptoms (Stippl et al., 2021).

This might be explained by ketamine's glutamatergic mechanism that stimulates intracellular signaling pathways substantially contributing to synaptic plasticity. Through its NMDA receptor antagonism ketamine causes a drastic elevation of glutamate levels, eventuating in an increased release of neurotrophic growth factors such as BDNF (brain-derived neurotrophic factor). Because of the essential role of these molecules in terms of synapse formation and maturation, this mechanism is considered as closely linked to ketamine's rapid antidepressant efficacy (Duman et al., 2016). Moreover, previous results indicate that the attenuating effect on cognitive symptoms might result from an enhanced prefrontal control obtained through rapid synaptogenesis (Gärtner et al., 2019). Along that line, our results indicate that pretreatment prefrontal brain activation is associated to cognitive symptom response following ketamine infusion.

Furthermore, our neuroimaging results showed no significant effects that survived Bonferroni correction concerning any other symptom dimension (i.e. affective or somatic). Nevertheless, uncorrected results indicated a reduced activation in the left amygdala and anterior insula prior ketamine as related to stronger reduction in affective symptoms 24 h post administration (see Table 4).

In addition, with specific focus on emotion processing during the WM task, on an uncorrected level, we found two regions positively correlating with cognitive symptom reduction: the right amygdala as well as the pgACC as illustrated in Fig.5. Again, no correlations were observed for the other two dimensions.

The amygdala as part of the limbic system is implicated in emotion regulation and important for the detection and response to emotional stimuli, next to the generation of negative mood states (Groenewold et al., 2013; Ma, 2015). MDD patients typically exhibit amygdala hyperactivation which is thought to result in rumination as a risk factor for depression and treatment resistance (Mandell et al., 2014). Furthermore, the amygdala is strongly interconnected with the prefrontal cortex and was shown to influence cognitive processing through emotional interference (Phelps, 2006). Congruently, our results indicate amygdala activation prior ketamine as associated with change following administration in either cognitive or affective symptoms depending on the focus of stimulation (i.e. WM or emotion processing).

The insula plays an important role in the processing of affective experiences (Craig, 2009) and is often hyperactive in depressive patients (Diener et al., 2012; Fitzgerald et al., 2008).
On this basis, our study results may thus indicate that lower activation in the left amygdala and insula in MDD patients at baseline not only indicates less deviant emotional processing but also predicts greater improvement in affective symptoms (Stippl et al., 2021).

The pgACC is also considered essential for emotion processing and regulation and is often hyperactive in MDD patients during rest (Jing et al., 2020). Previous evidence indicates that its task related activation might serve as potential response predictor for different kind of antidepressant treatments (Pizzagalli, 2011). Consistently, our findings might indicate that a pronounced beneficial effect of ketamine on cognitive symptoms is predicted by increased pgACC activation during emotion processing in the WM task.

At the whole brain level, no significant results were found that survived FDR correction. However, it is still worth noting that exploratory analysis at the uncorrected cluster level revealed several brain areas associated with symptom reduction in different BDI dimensions. Thereby, only negative associations were observed, with a lower level of baseline activation corresponding to a higher level of symptom reduction 24 hours after ketamine (see Table 5).

As this is the first study examining the effects of ketamine on BDI symptom clusters subsequently aiming to characterize predictors for symptom specific responses, we are confident that our findings substantially contribute to the state of the art research about ketamine's antidepressant efficacy. However, there are some limitations that merit consideration. Because this study is based on a naturalistic design, it does not include a placebo condition. Thus, it could be criticized that the results do not provide direct evidence of an effect that is specific to ketamine. Yet, it is known that ketamine has relatively strong psychotomimetic properties, potentially invalidating the benefits of a placebo condition (Short et al., 2018). Furthermore, because we wanted to investigate the effect of ketamine on different symptom dimensions, we state that the results can be successfully interpreted even without a placebo condition (Stippl et al., 2021). Because ketamine is pre-eminently given to severely depressed patients that have experienced treatment failure to at least one or more antidepressant therapies, no full restriction concerning psychopharmacological medication intake could be established. However, samples as such might give a more naturalistic clinical reflection and thus allow for an enhanced clinical utility than those of untreated patients.

Regardless of different affinities to the NMDA receptor and controversies about varying antidepressant efficacies, existing investigations differ with respect to the use of ketamine's R- and S-enantiomers (Andrade, 2017). The majority of studies thus far have been conducted with racemic ketamine, while in our sample some patients received S-ketamine. Nevertheless, the S-enantiomer has also proven good effect sizes in previous examinations (Singh et al., 2016).

Moreover, it could be considered that the subjective state assessed by the BDI, which is related to aberrant thoughts, is somewhat different than that related to neuropsychological performance. Nonetheless, previous studies provide evidence that in MDD, neuropsychological dysfunction is related to the "negative cognitive set" (Austin et al., 2001; Gupta et al., 2013), which is represented in BDI cognitive items such as self-criticism, self-rejection, and pessimism (Elliott et al., 1997).

Other findings in MDD patients indicate that negative feedback is associated with aberrant cognitive performance, suggesting an increased negative response bias to negative feedback. In this context, studies examining the impact of stimulus valence on cognitive performance have indicated that increased focus on negative stimuli is caused by aberrant information processing and emotional bias (Matt et al., 1992; Chamberlain and Sahakian, 2006; Murrough et al., 2011). In order to draw conclusions about the effect of ketamine on different symptom groups, our study includes a sufficiently large sample (N=47). fMRI scans, however, were obtained in a subsample of only 16 patients. Here, we examined BOLD reactivity before ketamine treatment in relation to a reduction in MDD symptoms. This experimental design has provided some insight into specific neuronal activation patterns that may be used to predict the effect of ketamine on specific symptoms. However, these outcomes need to be validated in a large independent patient sample.

With the inclusion of the aforementioned limitations, our accumulated results provide evidence that a single subanesthetic ketamine infusion has differential effects on MDD symptom dimensions, with the greatest reduction in symptom severity in the cognitive domain. Further, decreased deactivation of the DMN and increased activation of the DLPFC during a WM task at baseline might predict the predominant effect of ketamine on cognitive symptoms. These results not only indicate that a pro-cognitive mechanism might underlie the antidepressant effects of ketamine, but moreover suggest that this mechanism may be mediated by an increased potential for adaptive adjustments in the referred brain regions (Stippl et al., 2021).

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8. Statement of Authorship

„Ich, Anna Stippl, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema:
“Investigation of the effects of a single sub-anaesthetic ketamine infusion on symptoms of major depressive disorder and their association with neural activation patterns in cognition-emotion related brain areas - Die Untersuchung der Effekte einer einzelnen subanästhetischen Ketamininfusion auf Symptome der Major Depression und ihr Zusammenhang mit neuralen Aktivierungsmustern in Kognitions- und Emotions-assoziierten Gehirnarealen“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.
Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.
Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.
Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

9. Statement of Contribution

Anna Stippl hatte folgenden Anteil an der folgenden Publikation:

Stippl, A., Scheidegger, M., Aust, S., Herrera, A., Bajbouj, M., Gärtner, M.*, Grimm, S.* (2021). Ketamine specifically reduces cognitive symptoms in depressed patients: An investigation of associated neural activation patterns. J. Psychiatr. Res. 136, 402–408. https://doi.org/10.1016/j.jpsychires.2021.02.028
*These authors contributed equally

Beitrag im Einzelnen:

Im Rahmen meiner Promotion habe ich grundlegend zur Implementierung der Studienabläufe und der organisatorischen Infrastruktur am Standort Charité, Campus Benjamin Franklin beigetragen. Des Weiteren war ich für die konstante Kommunikation und Studienkorrespondenz mit den Stationen 16a/b, sowie 08a/b der Psychiatrie, Charité Campus Benjamin Franklin verantwortlich. Ich übernahm einen Großteil der Patientenakquise auf der Station, sowie die Koordination der fMRT-Termine. Ich habe mich um den Patiententransport von den besagten Klinikstationen zum MRT-Standort im Center for Cognitive Neuroscience (CCNB) der FU gekümmert. Dort betreute ich die fMRT-Messungen als „Advanced User“ und kümmerte mich um den Ablauf und die Versorgung der Patienten. Hierzu gehörte unter anderem die Aufklärung der Probanden und das Ausfüllen von Fremd- und Selbstbeurteilungsfragebögen mit den Patienten. Darüber hinaus bestand meine Aufgabe in der analogen und digitalen Archivierung von Probandendaten, sowie der quantitaven Aufbereitung in SPSS und Excel. Die Aufarbeitung der behavioralen Daten und deren statistische Auswertung habe ich selbstständig übernommen. Daraus entstanden Table.1 und Table.2, sowie Figure.1 der Publikation.
Gemeinsam mit der leitenden Professorin und dem Postdoktoranden der Forschungsgruppe habe ich die fMRT Daten mit SPM12 und REX in Matlab, sowie MRIcron und SPSS ausgewertet. Hierbei war ich hauptsächlich für die Aufarbeitung der fMRT-Bilder auf „Whole Brain“ Ebene, sowie auf „Region of Interest“ Ebene verantwortlich, während ich bei der Auswahl der statistischen Verfahren und der Interpretation Unterstützung erhielt. Daraus entstanden Figure.2, sowie Table.3 und Table.4.

Ich trug wesentlich dazu bei nach der passenden Literatur zu recherchieren und die Studie in den aktuellen Forschungstand einzuordnen. Darüber hinaus bin ich der alleinige Verfasser der ersten Version des Manuskriptes und war maßgeblich an der Korrespondenz zum mehrstufigen Peer-Reviewprozess vor Veröffentlichung des Papers beteiligt. Des Weiteren habe ich die Anfertigung und Präsentation eines E-Posters zu dieser Studie für den European Congress of Psychiatry 2020 selbstständig übernommen.

10. Extraction of Journal Summary List (ISI Web of KnowledgeSM)

Journal Data Filtered By: Selected JCR Year: 2019 Selected Editions: SCIE,SSCI Selected Categories: "PSYCHIATRY" Selected Category Scheme: WoS, Gesamtanzahl: 216 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1.	World Psychiatry	6,486	40.595	0.017130
2.	JAMA Psychiatry	13,433	17.471	0.056110
3.	Lancet Psychiatry	6,405	16.209	0.028290
4.	PSYCHOTHERAPY AND PSYCHOSOMATICS	4,275	14.864	0.006480
5.	AMERICAN JOURNAL OF PSYCHIATRY	41,967	14.119	0.034380
6.	MOLECULAR PSYCHIATRY	22,227	12.384	0.054730
7.	BIOLOGICAL PSYCHIATRY	44,016	12.095	0.053910
8.	JOURNAL OF NEUROLOGY NEUROSURGERY AND PSYCHIATRY	30,621	8.234	0.028510
9.	SCHIZOPHRENIA BULLETIN	17,703	7.958	0.027070
10.	BRITISH JOURNAL OF PSYCHIATRY	24,380	7.850	0.020520
11.	JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY	19,837	7.035	0.021080
12.	JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY	19,837	7.035	0.021080
13.	JOURNAL OF THE AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY	19,831	6.936	0.017840
14.	NEUROPSYCHOPHARMACOLOGY	26,281	6.751	0.040680
15.	BRAIN BEHAVIOR AND IMMUNITY	16,285	6.633	0.028560
16.	JOURNAL OF ABNORMAL PSYCHOLOGY	16,003	6.484	0.014170
17.	ADDICTION	19,861	6.343	0.030820
18.	Epidemiology and Psychiatric Sciences	1,584	5.876	0.004770
19.	PSYCHOLOGICAL MEDICINE	26,702	5.813	0.039350
20.	Clinical Psychological Science	2,599	5.415	0.011100

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
21.	BIPOLAR DISORDERS	4,838	5.410	0.006610
22.	ACTA PSYCHIATRICA SCANDINAVICA	13,539	5.362	0.011750
23.	Translational Psychiatry	9,160	5.280	0.029500
24.	Journal of Behavioral Addictions	2,184	5.143	0.005970
25.	CNS DRUGS	4,768	4.786	0.007670
26.	PSYCHONEUROENDOCRINOLOGY	19,287	4.732	0.027100
27.	DEPRESSION AND ANXIETY	9,355	4.702	0.013860
28.	AUSTRALIAN AND NEW ZEALAND JOURNAL OF PSYCHIATRY	7,192	4.657	0.008620
29.	Current Psychiatry Reports	4,785	4.539	0.010670
30.	EUROPEAN PSYCHIATRY	6,054	4.464	0.009470
31.	CURRENT OPINION IN PSYCHIATRY	4,182	4.392	0.006260
32.	JOURNAL OF PSYCHIATRY & NEUROSCIENCE	3,297	4.382	0.004290
33.	PROGRESS IN NEURO-PSYCHOPHARMACOLOGY & BIOLOGICAL PSYCHIATRY	11,179	4.361	0.013670
34.	PHARMACOPSYCHIATRY	1,787	4.340	0.001580
35.	INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY	6,749	4.333	0.011150
36.	npj Schizophrenia	502	4.304	0.002060
37.	JOURNAL OF CLINICAL PSYCHIATRY	18,652	4.204	0.018530
38.	WORLD JOURNAL OF BIOLOGICAL PSYCHIATRY	2,567	4.164	0.004200
39.	DRUG AND ALCOHOL DEPENDENCE	20,269	3.951	0.040630
40.	EUROPEAN CHILD & ADOLESCENT PSYCHIATRY	5,422	3.941	0.009450
41.	JOURNAL OF AFFECTIVE DISORDERS	32,869	3.892	0.055920
42.	SUICIDE AND LIFE-THREATENING BEHAVIOR	4,512	3.867	0.005980

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
43.	EUROPEAN NEUROPSYCHOPHARMACOLOGY	7,597	3.853	0.013120
44.	SCHIZOPHRENIA RESEARCH	22,003	3.759	0.030040
45.	JOURNAL OF PSYCHIATRIC RESEARCH	16,085	3.745	0.020560
46.	PSYCHOSOMATIC MEDICINE	12,560	3.702	0.009890
47.	PSYCHOSOMATIC MEDICINE	12,560	3.702	0.009890
48.	INTERNATIONAL JOURNAL OF EATING DISORDERS	9,613	3.668	0.010750
49.	Eating and Weight Disorders-Studies on Anorexia Bulimia and Obesity	1,977	3.634	0.002830
50.	Mindfulness	4,006	3.581	0.008500
51.	World Journal of Psychiatry	701	3.545	0.002190
52.	JMIR Mental Health	1,103	3.535	0.003440
53.	Internet Interventions-The Application of Information Technology in Mental and Behavioural Health	996	3.513	0.002720
54.	European Journal of Psychotraumatology	1,987	3.478	0.004940
55.	AMERICAN JOURNAL OF GERIATRIC PSYCHIATRY	7,144	3.393	0.009920
56.	AMERICAN JOURNAL OF MEDICAL GENETICS PART B-NEUROPSYCHIATRIC GENETICS	4,033	3.387	0.006040
57.	CNS SPECTRUMS	2,479	3.356	0.003480
58.	PSYCHIATRY AND CLINICAL NEUROSCIENCES	3,696	3.351	0.004260
59.	SOCIAL PSYCHIATRY AND PSYCHIATRIC EPIDEMIOLOGY	8,775	3.335	0.012760
60.	CANADIAN JOURNAL OF PSYCHIATRY-REVUE CANADIENNE DE PSYCHIATRIE	6,097	3.313	0.007620
61.	EUROPEAN ARCHIVES OF PSYCHIATRY AND CLINICAL NEUROSCIENCE	4,136	3.288	0.004760
62.	BEHAVIOR THERAPY	5,758	3.243	0.006320
63.	PSYCHOPHARMACOLOGY	22,417	3.130	0.019820
64.	JOURNAL OF PSYCHOPHARMACOLOGY	6,262	3.121	0.009340

11. Selected Bibliography

Ketamine Specifically Reduces Cognitive Symptoms in Depressed Patients: An Investigation of Associated Neural Activation Patterns

Stippl, A., Scheidegger, M., Aust, S., Herrera, A., Bajbouj, M., Gärtner, M.*, Grimm, S.*
*These authors contributed equally

Journal of Psychiatric Research 136 (April): 402–8.
https://doi.org/10.1016/j.jpsychires.2021.02.028.

Impact Factor: 3.745

Stippl, A., Scheidegger, M., Aust, S., Herrera, A., Bajbouj, M., Gärtner, M., Grimm, S., 2021. Ketamine specifically reduces cognitive symptoms in depressed patients: An investigation of associated neural activation patterns. J. Psychiatr. Res. 136, 402–408. https://doi.org/10.1016/j.jpsychires.2021.02.028

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12. Curriculum Vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht

13. Complete list of publications

Carstens, L., Hartling, C., Aust, S., Domke, A.-K., Stippl, A., Spies, J., Brakemeier, E.-L., Bajbouj, M., & Grimm, S. (2021). EffECTively Treating Depression: A Pilot Study Examining Manualized Group CBT as Follow-Up Treatment After ECT. *Frontiers in Psychology*, *12*, 3662. https://doi.org/10.3389/fpsyg.2021.723977
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Carstens, L., Hartling, C., Stippl, A., Domke, A.-K., Herrera-Mendelez, A. L., Aust, S., Gärtner, M., Bajbouj, M., & Grimm, S. (2021). A symptom-based approach in predicting ECT outcome in depressed patients employing MADRS single items. *European Archives of Psychiatry and Clinical Neuroscience*. https://doi.org/10.1007/s00406-021-01301-8
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Gärtner, Matti, M. Elisabetta Ghisu, Milan Scheidegger, Luisa Bönke, Yan Fan, Anna Stippl, Ana-Lucia Herrera-Melendez, et al. 2018. 'Aberrant Working Memory Processing in Major Depression: Evidence from Multivoxel Pattern Classification'. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology* 43 (9): 1972–79. https://doi.org/10.1038/s41386-018-0081-1.
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Herrera-Melendez, Ana, Anna Stippl, Sabine Aust, Milan Scheidegger, Erich Seifritz, Isabella Heuser-Collier, Christian Otte, Malek Bajbouj, Simone Grimm, and Matti Gärtner. 2021. 'Gray Matter Volume of Rostral Anterior Cingulate Cortex Predicts Rapid Antidepressant Response to Ketamine'. *European Neuropsychopharmacology* 43 (February): 63–70. https://doi.org/10.1016/j.euroneuro.2020.11.017.
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Stippl, A., M. Scheidegger, S. Aust, A. Herrera, M. Bajbouj, M. Gärtner, and S. Grimm. 2021. 'Ketamine Specifically Reduces Cognitive Symptoms in Depressed Patients: An Investigation of Associated Neural Activation Patterns'. *Journal of Psychiatric Research* 136 (April): 402–8. https://doi.org/10.1016/j.jpsychires.2021.02.028.
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Stippl, Anna, Fatma Nur Kirkgöze, Malek Bajbouj, and Simone Grimm. 2020. 'Differential Effects of Electroconvulsive Therapy in the Treatment of Major Depressive Disorder'. *Neuropsychobiology* 79 (6): 408–16. https://doi.org/10.1159/000505553.
Impact Factor: 2.328

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