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# General and emotion-specific neural effects of ketamine during emotional memory formation

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ABSTRACT

Animal studies suggest that N-methyl-D-aspartate receptor (NMDAR) dependent signalling in limbic and prefrontal regions is critically involved in both cognitive and emotional functions. In humans, ketamine-induced transient, and disorder associated chronic NMDAR hypofunction (i.e. in schizophrenia) has been associated with deficient performance in the domains of memory and higher-order emotional functioning, as well as altered neural activity in the underlying limbic-prefrontal circuits. To model the effects of NMDAR hypofunction on the integration of emotion and cognition the present pharmacological fMRI study applied the NMDAR antagonist ketamine (target plasma level=100 ng/ml) to 21 healthy volunteers in a within-subject placebo-controlled crossover design during encoding of neutral, positive and negative pictures. Our results show that irrespective of emotion, ketamine suppressed parahippocampal and medial prefrontal activity. In contrast, ketamine selectively increased amygdala and orbitofrontal activity during successful encoding of negative stimuli. On the network level ketamine generally increased medial prefrontal-parahippocampal coupling while specifically decreasing amygdala-orbitofrontal interplay during encoding of negative stimuli. On the behavioural level, ketamine produced generally decreased memory performance and abolished the emotional enhancement of memory after a wash-out period of 5 days. The present findings suggest that ketamine produces general as well as valence-specific effects during emotional memory formation. The pattern partly overlaps with alterations previously observed in patients with schizophrenia.

## Introduction

N-methyl-D-aspartate receptors (NMDAR) are widely distributed throughout the brain, with particular high densities in frontal and limbic regions involved in cognition, including memory processing, and emotion (Fletcher and Henson, 2001; Lepage et al., 1998; Walter et al., 2014; Riedel et al., 2003; Phan et al., 2002; Etkin et al., 2011). Animal studies consistently revealed that experimental application of competitive or non-competitive NMDAR antagonists transiently disrupts memory performance (Puma et al., 1998), with particularly pronounced effects when the drug interfered with the acquisition of novel information (Newcomer et al., 2000). In recent years pharmacological studies in humans have increasingly employed the non-competitive NMDAR antagonist ketamine as a translational model to explore the behavioural and neural effects of NMDAR-hypofunction (Stone et al., 2009). The observed detrimental effects of ketamine administration on cognitive performance, including memory (Krystal et al., 1994, Newcomer et al., 1999, Hetem et al., 2000), closely resemble those observed in animal models. Results from functional MRI (fMRI) further suggest that ketamine administration in humans influences, and interferes with, the underlying memory-related neural circuitry (Honey et al., 2005; Wong et al., 2016, Grimm et al., 2015).

Recent animal work emphasizes an involvement of NMDAR-dependent signalling in medial prefrontal cortex (mPFC) and amygdala

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during emotional processing and emotion-cognition interactions, including emotional learning (Vieira et al., 2015; Hegoburu et al., 2014; Masneuf et al., 2014). These are in line with studies in humans which revealed emotion-specific disruptions during facial emotion encoding and recognition, as well as altered amygdala and prefrontal functioning following ketamine-induced NMDAR blockade (Ebert et al., 2012; Schmidt et al., 2013, Abel et al., 2003). The potential involvement of the NMDAR in emotion processing is further substantiated by the rapid antidepressant effect of single-dose administrations of ketamine in treatment-resistant depression (Aan Het Rot et al., 2012; Zarate et al., 2006).

In addition to its potential involvement in depression, altered NMDAR-signalling has been suggested to play a critical role in the pathophysiology of schizophrenia (Krystal et al., 2003). Initial observations that NMDAR antagonists, including ketamine, produce psychotomimetic symptoms and cognitive disruptions similar to those observed in schizophrenia patients (Krystal et al., 1994; Corlett et al., 2011) resulted in a NMDAR hypofunction model of schizophrenia (e.g. Jentsch and Roth 1999). Schizophrenia is a complex neuropsychiatric disorder characterized by marked impairments in cognitive and emotional domains (Bleuler, 1950). Neuropsychological studies consistently revealed cognitive (Heinrichs and Zakzanis, 1998; Reichenberg and Harvey, 2007), particularly memory (Mesholam-Gately et al., 2009), deficits in patients with schizophrenia. Dysfunctions in the emotional domain have gained increasing attention during the last years, with meta-analytic data suggesting marked impairments in higher-order emotional processing in schizophrenia patients (Marwick and Hall, 2008; McCleery et al., 2015). In contrast, findings regarding disruptions in basic emotional processing remain less clear. Whereas some studies revealed that schizophrenia patients retrospectively report decreased levels of positive and increased levels of negative emotional experience (Cohen and Minor, 2008; Blanchard et al., 1998), immediate emotional experience have been found to be intact (Aleman and Kahn, 2005; Kring and Moran, 2008). These contradictory findings might point to a disintegration of emotion and cognition in schizophrenia, where immediate emotional experiences are intact, however, the impact of emotional experience on memory is disrupted.

Current concepts of emotion-memory interactions hold that memory for emotional information is enhanced relative to neutral information (Dolcos et al., 2004; La Bar and Cabeza, 2006). Neuroimaging studies on encoding of neutral (Kim, 2011) and emotional information (Murty et al., 2010; Hermans et al., 2014) indicate a high overlap between NMDAR-rich regions and the emotional memory networks, with successful encoding being associated with increased activity in hippocampal, fusiform and prefrontal regions (subsequent memory effect, SM), and the enhancement of emotional relative to neutral information being dependent on the hippocampal formation and the amygdala (emotional subsequent memory effect, ESM). A number of studies examined the ESM in schizophrenia patients to specifically probe the disintegration of emotion and cognition (Herbener, 2008). Most ESM studies observed normal emotional experience during encoding in schizophrenia patients (Lakis et al., 2011; Herbener et al., 2007; Hall et al., 2007), however, with regard to the specificity of impairments in the domain of the emotional subsequent memory effect findings remained inconsistent ranging from unspecific impairments (Lakis et al., 2011; Hall et al., 2007) to highly selective impairments for positive information only (Herbener et al., 2007).

Based on accumulating evidence for a critical role of NMDAR-signaling in both cognition and emotion, initial pharmacological fMRI evidence for emotion-specific effects of ketamine-induced transient NMDAR hypofunctioning (Abel et al., 2003; Scheidegger et al., 2016) and findings in schizophrenia patients with a putative NMDAR hypofunctioining it is hypothesized that experimentally induced NMDAR hypofunctioning in healthy subjects might (1) disrupt emotion-cognition interaction during emotional memory formation, and (2) produce a pattern of general as well as emotion-specific neural effects. To this end, the present randomized within-subject placebo-controlled crossover design combined the application of ketamine versus placebo during emotional memory formation with fMRI. To control for (sub-)acute effects of ketamine on recognition participants underwent a 5-day washout period before the assessment of emotional memory performance. Based on previous findings we expected that ketamine administration would abolish the emotional enhancement of memory and suppress amygdala-hippocampal activity during emotional memory formation mirroring disintegration of emotional experience on memory formation.

## Material and methods

### *Participants*

Healthy, non-smoking, right-handed male volunteers with normal verbal intelligence as assessed by the Mehrfachwahl-Wortschatz-Intelligenztest (MWT-b, Lehrl, 2005) were recruited at the University of Bonn, Germany. Prior to study inclusion all participants were thoroughly screened for exclusion criteria. Study-specific exclusion criteria included MRI contraindications, current or previous history of axis I disorders according to the DSM IV criteria (assessed by the MINI, Ackenheim et al., 1999), diagnosis of psychotic disorders among first degree relatives, neurological or cardiovascular disorders, history of illicit drug use, head-injuries, body mass index (BMI) < 19 or > 25, regular use of medication, use of psychoactive substances in the 7 days prior to the experiment (validated via urine sample and enzyme-multiplied immunoassay, nal von minden GmbH, Regensburg, Germany). Participants were instructed to maintain their regular sleep and wake cycles before the experiment, and to abstain from food intake during the 6 h preceding treatment. Participants received monetary compensation for study participation. The study had ethical approval of the local ethics committee at the University of Bonn and was in accordance with the latest revision of the Declaration of Helsinki. All participants provided written informed consent before study inclusion.

From a total of 43 volunteers assessed for study eligibility 29 met the study-specific criteria and were enrolled in the study. Participants data were excluded from all further analyses in case participants failed to attend the second pharmaco-fMRI assessment (n=2), were not able to adhere to the 5-day post pharmaco-fMRI memory assessment interval (n=2), misunderstood the instructions (n=1), or showed head-movements > 3mm during fMRI (ketamine, 2; placebo, 1). The final study sample (n=21) had an average age of 25.1 ( ± 3.5) years, 17.5 ( ± 2.8) years of education, and an estimated verbal IQ of 111 ( ± 7.4).

### *Study protocols*

Effect of ketamine on emotional memory formation and subsequent recognition performance were assessed by embedding a pharmacological fMRI (pharmaco-fMRI) experiment in a double-blind randomized within-subject placebo-controlled crossover design. To control for order effects the order of ketamine and placebo administration was counterbalanced across participants, pharmaco-fMRI assessments were separated by ≥ 7 days and administered at the same time of the day ( < 1.5 h difference). Immediately before the start of the pharmaco-fMRI experiments subjects were screened by an experienced anaesthesiologist (C.N.), the anaesthesiologist also continuously monitored the vital signs of the participants during pharmaco-fMRI using an MRI-compatible pulse oximeter and a supervised post-scanning period. In line with previous ketamine-induced model psychosis experiments (Schmechtig et al., 2013) participants received either racemic ketamine (Ketamin-Ratiopharm 500, injection solution, Ratiopharm©, Ulm, Germany) or placebo (0.9% saline solution, Ratiopharm©, Ulm, Germany) via identical 1-h application protocols by means of a