Do NMDA-R Antagonists Re-Create Patterns of Spontaneous Gamma-Band Activity in Schizophrenia? A Systematic Review and Perspective

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Introduction

Despite more than a hundred years of research, the pathophysiological processes that underlie the circuit dysfunctions that give rise to the symptomatic manifestation of schizophrenia (ScZ) remain to be determined. While aberrant dopaminergic neurotransmission has received considerable attention and remains the primary target for anti-psychotic medications (Howes and Kapur 2009), more recently a primary dysfunction in the glutamate system has been proposed to account for the developmental profile and cognitive dysfunctions associated with the disorder (Abi-Saab et al., 1998; Coyle, 2012; Kantrowitz and Javitt, 2010; Kim et al., 1980).

Specifically, hypofunctioning of the N-methyl-d-aspartate receptor (NMDA-R) has been considered a key process in the pathophysiology of ScZ (Olney et al., 1999; Phillips and Silverstein, 2003). NMDA-Rs are diverse in subunit composition, biophysical, and pharmacological properties and are involved in several important circuit and behavioural properties, including learning, plasticity and memory (Paoletti et al., 2013). Importantly, NMDA-Rs are found throughout cortical and sub-cortical areas although differences in regional expression profiles exist (Zilles and Palomero-Gallagher, 2017).

Evidence for the involvement of NMDA-Rs in the pathophysiology of ScZ came from studies into the effects of NMDA-R antagonists, such as Ketamine and Phencyclidine (PCP), in healthy volunteers (Allen and Young, 1978; Krystal et al., 1994). These studies showed that the full spectrum of psychopathological symptoms observed in ScZ (Krystal et al., 1994) as well as selective cognitive deficits (Umbricht et al., 2000) could be elicited transiently by administration of NMDA-R antagonists. More recently, studies using functional magnetic resonance imaging (fMRI) showed that alterations in resting-state activity induced by acute Ketamine administration

in healthy volunteers resemble those observed in ScZ, in particular during the early stages (Anticevic et al., 2015; Braun et al., 2016; Driesen et al., 2013).

Evidence from non-invasive neuroimaging is complemented by data examining the expression of NMDA-Rs in post-mortem tissue in ScZ-patients. A reduction in the NR1 subunit in the PFC (Catts et al., 2016), but also in other NMDA-R subunits have been reported (Akbarian et al., 1996; Kornhuber et al., 1989; Weickert et al., 2013). Moreover, there are findings to suggest that the reduction of NMDA-Rs may be pronounced in interneurons that are enriched for GAD(67) mRNA (Woo, et al., , 2004), the main enzyme that synthesizes GABA, providing evidence for the hypothesis that the excitatory drive onto interneurons is disturbed in ScZ. Finally, recent genetic evidence has also shown that Copy Number Variants substantially increase susceptibility to schizophrenia are enriched for NMDA-Rs (Pocklington et al., 2015).

In addition, acute and chronic administration of NMDA-R antagonists in animal models have re-recreated circuit dysfunctions as well as behavioural and cognitive deficits observed in ScZ-patients (Kantrowitz and Javitt, 2010; Phillips and Silverstein, 2003). One hypothesis to account of these effects are the consequences of NMDA-R hypofunction on γ-Aminobutyric acid (GABA)ergic interneurons (Cohen et al., 2015; Lisman et al., 2008). In particular, transient blockade of NMDA-Rs is associated with a reduced activation of interneurons which in turn leads to a disinhibition of pyramidal cells (Homayoun and Moghaddam, 2007). Accordingly, one hypothesis is that NMDA-R hypofunctioning in ScZ leads to a shift in the balance between Excitation/Inhibition (E/I-Balance) across cortical and subcortical networks (Lisman et al., 2008; Uhlhaas and Singer, 2012, Rivolta et al., 2014).

One important manifestation of alterations in E/I-balance are changes in the patterns of rhythmic activity (Deco et al., 2014). During normal brain functioning, amplitude and organisation of neural oscillations are closely depended upon GABAergic interneuron-mediated inhibition of pyramidal

cell activity that regulate the output of cell-assemblies leading to rhythmic fluctuations in neural excitability (Sohal et al., 2009; Kopell and LeMasson, 1994). Of particular interest are oscillations in the gamma-band range between 30-200 Hz as extensive evidence exist on the circuit mechanisms involved (Buzsaki and Wang, 2012) and the tight correlations between the occurrence of gamma-band oscillations and perceptual as well as cognitive processes (Fries, 2009). Specifically, parvalbumin-expressing (PV+) (GABA)ergic interneurons have been involved in the generation of high-frequency oscillations (Sohal et al., 2009) as well α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)- and NMDA-R-mediated activation of PV+ interneurons (Carlén et al., 2012; Fuchs et al., 2007).

Accordingly, given the close correlations between E/I-balance parameters and gamma-band activity as well as the evidence for the role of NMDA-Rs in the pathophysiology of ScZ, we hypothesized that NMDA-R hypofunction should induce alterations in the amplitude and organisation of high-frequency oscillations that are closely related to disturbances observed in ScZ. To test this hypothesis, we carried out a systematic review that compared the changes elicited by NMDA-R antagonists in human and pre-clinical recordings on fluctuations in gamma-band power with the pattern observed in resting-state electro/magnetoencephalographic (EEG/MEG)-recordings obtained from clinical high-risk for psychosis (CHR-P), first-episode psychosis (FEP) and chronic ScZ-patients. As a secondary objective, we also examined the effect of NMDA-antagonists on functional connectivity. We identified n = 24 pre-clinical (monkey: n = 1, rodent: n = 23) and n = 9 human studies that examined the effects of NMDA-Rs antagonists on spontaneous gamma-band oscillations. Of these, 8 studies (n = 6 preclinical and n = 2 human) reported data on functional connectivity changes. These studies were then compared to resting-state EEG/MEG-data obtained from CHR-P (n = 3), FEP (n = 10) and chronic ScZ-patients (n = 19) .

Method

PubMed and Google Scholar were searched for publications with the following search terms for the preclinical literature: ‘Preclinical’, ‘Ketamine’, ‘PCP’, ‘MK801’, ‘NMDA’, ‘Gamma’, ‘until August 2019. For human studies investigating the effects of Ketamine on gamma-band oscillations, ‘Human’, ‘Ketamine’, ‘NMDA’, ‘Gamma’ were entered. Finally, studies that examined gamma-band oscillations in resting state EEG/MEG-data as well as EEG, Local Field Potentials (LFP) and Electrocorticography (EcoG) for preclinical studies were identified with the search terms: ‘Resting state’, ‘EEG/MEG’, ‘EEG/LFP/EcoG’. Moreover, the reference lists of relevant articles were searched for studies matching our search criteria. Results from all search terms were combined and PMIDs (unique identifier number used in PubMed) were used to exclude duplicates. The titles and abstracts of each publication were carefully inspected. Reviews, meta-analysis, case studies and case reports were also excluded from the sample.

Inclusion criteria for pre-clinical studies on NMDA-R antagonists were as follows: 1) exclusively Ketamine, PCP and/or MK801 administration, 2) in vivo studies, 3) subanaesthetic dosage and 4) EEG/LFP/EcoG-recordings. For human Ketamine studies, inclusion criteria were: 1) EEG/MEG-recordings, 2) no psychotropic medication, 3) no psychiatric/substance abuse history, and 4) sample size of 10 or more participants. Finally, inclusion criteria for EEG/MEG-studies in ScZ-patients were as follows: 1) EEG/MEG, 2) sample size of 10 or more patients and 3) a healthy control group.

Crucially, only studies were considered that investigated gamma-band oscillations during resting-state activity independent of task-demands. Thus, studies were not included, for example, that investigated baseline-changes during sensory or cognitive tasks.

The following information was retrieved from pre-clinical studies: number and type of animals, recording, frequency range and drug type and dosage. For human Ketamine studies, we identified number of participants, recording, frequency range and drug dosage. Finally, patient type (CHR-P, FEP vs. chronic ScZ), age and sex of participants, medication status, recording and frequency range were retrieved for patient studies.

Data extraction

The data for each of the included studies were extracted by BB and supervised by PU. When effect sizes were missing from the reviewed articles, the authors were contacted to request the relevant data.

Statistical analysis

Non-parametric Kruskal-Wallis test and Chi-square corrected Fisher-Freeman-Halton Exact Test were conducted to identify parameters associated with studies reporting either upregulation, downregulation or no significant difference for gamma-band activity in the ScZ group compared to controls (Table 2).

For the estimation of effect sizess, the Comprehensive Meta-Analysis (CMA) software version 2.0 was used. Hedges' g was calculated based on mean scores of gamma-band power values. When these values were not reported, exact F-, t- or p-values were used. Overall, effect size analysis was conducted solely on ScZ studies due to lack of sufficient data from preclinical and Ketamine-studies in human participants.

For studies in ScZ-patients, effect size data was available in n = 22 studies out of 27. We used R (Team R, 2013) to plot the standardized mean differences with 95% confidence intervals. Funnel plots were visually inspected for symmetry to assess publication bias and outliers. Egger's regression test, performed in R (Team R, 2013; Sterne and Egger, 2001; Schwarzer, 2007) were used to assess potential asymmetry and interpreted (Cohen, 1988).

Furthermore, risk of bias and quality of studies were assessed following Cochrane risk of bias guidelines (Higgins, 2008) for healthy human randomised-controlled studies, SYRCLE's risk of bias tool for animal studies (Hooijmans, et al., 2014) and the ROBINS-I assessment tool (Sterne et al., 2016) for matched-cohort studies in ScZ population.

Results

Study selection

Preclinical Studies: 137 records were identified of which 72 were excluded after abstract screening. The remaining 65 articles were assessed for eligibility based on our criteria and 40 studies were excluded bringing the sample to 25 studies. Of the 43 studies excluded, 12 administered anaesthetic dosages of NMDA-R antagonists, 10 studies did not report resting-state data, 9 studies included additional drugs other than NMDA-R antagonists, 7 included genetically modified animals, 4 included ex-vivo experiments and one study did not perform recordings immediately after drug infusion. During the preparation of the manuscript, 2 more studies meeting our inclusion criteria were identified after the initial selection (see Figure 1), bringing the final total to 24 studies.

Human Studies: Only studies that examined the effects of Ketamine, MK801 and PCP in healthy volunteers were included. Thus, EEG/MEG-data that involved patients with Major Depression Disorder (MDD) were not considered. 79 records were identified initially by searching for the key terms in the database, of which 48 were excluded after abstract screening. The remaining 31 articles were assessed for eligibility based on our criteria and 22 studies were excluded. Of these 22 studies, 11 did not report of resting-state data, 5 studies included only a clinical population, 4 administered anaesthetic dosage and 2 included additional drugs to NMDA-R antagonists.

Resting-State EEG/MEG studies in ScZ: 289 records were identified of which 148 were excluded after abstract screening. The remaining 143 articles were assessed for eligibility based on our criteria and 115 studies were excluded. Of these 115 studies, 39 did not include analysis of gamma-band frequencies, 21 consisted of pharmacological studies, 36 did not report resting-state data, 12

studies a clinical group other than ScZ diagnosis (i.e. MDD, bipolar disorder etc.) and 7 studies had a clinical sample smaller than n = 10. During the preparation of the manuscript, 5 additional studies meeting our inclusion criteria were included after the initial selection (Krukow et al., 2019; 2020; Lottman et al., 2019; Tanaka-Koshiyama et al., 2020; Zeev-Wolf et al., 2018) (see Figure 3). N = 6 studies that employed only visual artefact correction procedures were excluded (Mitra et al., 2015; Tikka et al., 2013, 2015, 2016; Umesh et al., 2018; Winterer et al., 2001). This is because ocular and muscular artefacts in electrophysiological recordings closely overlap with neuronal high frequency activity (e.g., Shackman et al., 2009; Whitham et al., 2007; Yuval-Greenberg et al., 2008). Accordingly, rigorous artefact identification procedures, such Independent Component Analysis (ICA), are of particular importance for EEG-recordings (Fries et al., 2008, Schwartzman and Kranczioch, 2011).

Study Characteristics: Preclinical Studies of NMDA-R Antagonists

Of the 24 studies (Table 1), 21 studies examined NMDA-R antagonists in rats while the remaining studies were performed in monkeys (n = 1) and mice (n= 2). The majority of studies were performed in male animals (n = 23); while no data regarding sex was available for n = 1 study (Molina et al. 2014). N = 23 studies were conducted in freely-moving animals. N = 19 studies administered Ketamine, 14 MK-801 and 3 PCP of which the majority where in adult animals (adult: n = 20, n = 2 pre-adolescence, for n = 2 studies no data was available). N = 22 studies administered NMDA-antagonists acutely (single or up to 5 administrations with washout periods ranging from 24 hours to 7 days), while two studies (Kittelberger et al., 2012; Sampaio et al., 2018) tested both acute and chronic applications of NMDA-antagonists. Recording techniques included LFPs) (n = 13), ECOG (n = 4) and iEEG-recordings (n = 7).

N = 18 studies recorded brain activity in cortical areas (unspecified = 1; frontal: n = 17, occipital: n = 3, parietal: n = 5, temporal n = 2; some overlap) and n = 15 studies recorded subcortical structures (hippocampus: n = 8, striatum: n = 2, basal ganglia n =2, nucleus accumbens: n = 2, thalamus: n = 1, forebrain= 1, globus pallidus = 1), n = 8 studies of which obtained both cortical and subcortical recording. All studies examined power modulation following NMDA-R antagonists (n = 27) while 6 studies also examined measures of functional connectivity. Definition of gamma-band frequencies varied across studies (see Table 1). Accordingly, we differentiated between studies that examined activity in the lower (30-60 Hz) (all studies; n = 27) and high gamma-band range (> 60 Hz) (n = 21 studies).

Study Characteristics: Human Ketamine EEG/MEG-studies

The majority of studies utilized a crossover design except one study in which all participants underwent the same protocol, consisting of a single constant subanaesthetic dose of Ketamine (Li and Mashour, 2019) (Table 2). Only male participants were recruited in 6 studies (de la Salle et al., 2016; Forsyth et al., 2018; McMillan et al., 2019; Muthukumaraswamy et al., 2015; Sanacora et al., 2014; Zacharias et al., 2019). In addition, 6 studies employed an initial bolus of Ketamine followed by a constant Ketamine infusion (de la Salle et al., 2016; Forsyth et al., 2018; McMillan et al., 2019; Muthukumaraswamy et al., 2015; Rivolta et al., 2015; Zacharias et al., 2019), while the remaining studies administered only a constant subanaesthetic infusion (Li et al., 2019; Nugent et al., 2019; Sanacora et al., 2014). Ketamine infusion varied between .25 -.65 mg/kg. Six studies used EEG (De la Salle, 2016; Forsyth et al., 2018; Zacharias et al., 2019; Li and Mashour, 2019; McMillan et al., 2019; Sanacora et al., 2014) while 3 studies employed MEG (Nugent et al., 2019; Muthukumaraswamy et al., 2015; Rivolta et al., 2015). MacMillan et al. (2019) acquired EEG-data during a fMRI-recording. Most studies obtained amplitude estimates of EEG/MEG-data at

both sensor and source-level. N = 2 studies reported connectivity analysis of MEG-data (Muthukumaraswamy et al., 2015; Rivolta et al., 2015). N = 5 studies examined both low (30-60 Hz) and high gamma-band (> 60 Hz) activity while the remaining studies (n = 4 studies) reported only 30-60 Hz power modulation.

Study Characteristics: EEG/MEG Resting-State in ScZ

Of the 27 studies, 19 studies included chronic schizophrenia patients, 10 examined FEP-patients, 3 CHR-P participants (Table 3). N = 17 studies used EEG, while 8 employed MEG (Escudero et al., 2013; Grent't-Jong et al., 2018; ; Kim et al., 2014; Kissler et al., 2000; Lottman et al., 2019; Popov and Popova, 2015; Rutter et al., 2009; Zeev-Wolf et al., 2018). Eyes-closed recordings were obtained in n = 19 studies, the remaining obtained EEG/MEG-data during an eyes-open condition (n = 7 studies). One study obtained both eyes-open and eyes-closed data (Venables et al., 2009). While most studies reported data from medicated ScZ patients (n = 19), n = 6 studies reported data from unmedicated patients (Arikan et al., 2018; Bandyopadhyaya et al., 2011; Grent't-Jong et al., 2018; Strelets et al., 2006; Ramyead et al., 2015; Takahashi et al., 2018). Fourteeen studies reported symptom correlations. The majority of studies obtained amplitude estimates of EEG/MEG-data at sensor-level (n = 15), while n = 10 studies used source estimates (see Table 3) and n = 2 studies reported only connectivity results (Krukow et al., 2018; 2019). In addition, n = 14 studies reported sensor-level (n = 10) and source-level (n = 4) connectivity analysis. N = 27 studies reported low gamma-band and n = 10 studies reported activity in the high gamma-band. Different methodologies were employed for artefact rejection across studies: n = 12 studies used ICA, while n = 3 studies used PCA (see Table 3).

Risk of bias within and across studies

Preclinical Ketamine Studies

N = 22 included a vehicle condition, while n = 2 studies used a single dose of Ketamine (Cordon et al., 2015; Slovik et al., 2017). Thirteen studies presented a crossover design, n = 8 studies employed a between-subject design (Hakami et al., 2015; Kittelberger et al., 2018; Ma and Leung, 2007; Nagy et al., 2016; Sampaio et al., 2017; Torres et al., 2010; Wróbel et al., 2020) and the remaining n = 4 studies included a single observational group in which all animals underwent the same protocol (Caixeta et al., 2013; Cordon et al., 2015 ; Nicolas et al., 2011; Slovik et al., 2017). Of the included studies, n = 14 were considered at low overall risk of bias, n = 5 were considered at unclear overall risk of bias (Caixeta et al., 2013; Lee et al., 2017; Molina et al., 2014; Pinault, 2008; Slovik et al., 2017) and n = 5 were considered at high overall risk of bias (Hakami et al., 2015; Kittelberger et al., 2018; Ma and Leung, 2007; Philips et al., 2011; Wróbel et al., 2020; Torres et al., 2010) (See Table 1 in Supplementary Material).

Human Ketamine Studies

N = 8 studies were placebo-controlled, n = 4 studies reported double-blinding and randomisation (de la Salle et al., 2016; Nugent et al., 2019; Sanacora et al., 2014; Zacharis et al., 2019), 4 studies reported single-blinding and randomization (Forsyth et al., 2018; McMillan et al., 2019; Muthukumaraswamy et al., 2015; Rivolta et al., 2015), while Li and Mashour (2019) study reported no blinding and included solely one observational group of healthy controls who underwent the same protocol consisting of one EEG-recording during a single administration of Ketamine. Overall, n = 5 were considered at low overall risk of bias, n = 2 studies (Li and Mashour, 2019; Muthukumaraswamy et al., 2015) presented high overall risk of bias and n = 2 (Forsyth et

al., 2018; Rivolta et al., 2015) were considered at unclear risk of bias (See Table 2 in Supplementary Material).

Schizophrenia Resting-state Studies

Twenty-five out of n = 27 studies were matched-cohort studies, while in two studies (Arikan et al., 2018; Baradits et al., 2019) ScZ-patients and controls were not individually matched by age, gender and education level. N = 7 studies were considered to have high overall risk of bias (Arikan et al., 2018; Bandyopadhyaya et al., 2011; Baradits et al., 2019; Escudero et al., 2013; Garakh et al., 2015; Kam et al., 2013; Zeev-Wolf et al., 2018), n = 6 were considered at unclear risk (Kissler et al., 2000; Krukow et al., 2019; Lottman et al., 2019; Popov and Popova, 2015; Rutter et al., 2009; Takahashi et al., 2018). The remaining n = 14 studies showed low risk of bias. (See Table 3 in Supplementary material for quality assessment of schizophrenia resting-state studies).

Risk of publication bias

Egger's regression test was not significant ($t = 0.2439$, $df = 20$, $p = 0.8098$), suggesting no publication bias.

Effects of NMDA-Antagonists on Gamma-Band Oscillations in Preclinical studies

NMDA-antagonists (Ketamine, PCP and MK801) were associated with an increase in gamma-band power in the majority of the preclinical studies included (n =20). No effect of NMDA-R antagonists on gamma-band power and coherence was reported by Torres et al. (2010). Mixed findings emerged from n = 3 studies (Hunt et al., 2010; Kittelberger et al., 2012; Hiyoshi et al., 2014). Hunt et al. (2010) observed an increase in high-frequency oscillations following MK801 at

low dosages while a decrease was found at higher dosages . Hiyoshi et al. (2014) reported a dose dependent effect following Ketamine, PCP and MK801 administration, characterised by an increase in gamma-band at lower dosages and a decrease at higher doses. Mixed results also emerged from Kittelberger et al. (2012) who reported a difference between acute and chronic administration. Specifically, gamma-band activity increased following acute dosage while decreasing after chronic Ketamine and MK801 administration. Importantly, no systematic differences were observed for different NMDA-R antagonists (PCP, MK-801, Ketamine) on gamma-band activity [N = 34 (100%); p = .450].

No systematic difference emerged from dosages of NMDA-R antagonists across preclinical studies on the amplitude of gamma-band activity [$\chi 2(1, N = 10) = 3.6$, p = .109]. Thus, n = 10 preclinical studies investigated the effects of increasing dosages of NMDA-antagonists on the amplitude of gamma band oscillations. A dose-dependent modulation of gamma-band activity was observed in n = 2 studies (Hiyoshi et al. 2014; Hunt et al. 2010), while the remaining studies found no change in gamma-band power following increased dosages (Caixeta et al. 2013; Hakami et al. 2009; Hansen et al. 2018; Lee et al. 2017; Nagy et al., 2016; Nicolas et al. 2011; Pinault 2008; Sampaio et al., 2018).

Out of 8 studies, n = 3 studies found frequency dependent effects. Ji et al. (2013) observed an increase for 30-80 Hz power and no effect for 80-150 Hz activity. Similarly, Cordon et al. (2015) found a ketamine-related effect for only for 80 Hz power. Finally, in the study by Sampaio et al. (2018), Ketamine increased 50-100 Hz power at all dosages, while in the 30-50 Hz range only 10 or 50 mg/kg but not 100 mg/kg showed a significant increase.

Connectivity analysis was conducted in n = 6 out of = 27 studies (Caixeta et al. 2013; Cordon et al. 2015; Kjaerby et al. 2017; Nicola et al., 2011; Slovik et al., 2017; Torres et al. 2010). While Torres et al. (2010) showed no changes in gamma-band coherence following ketamine

administration, the remaining n = 5 studies all reported an increase in gamma-band connectivity (sensor-level in all studies).

Of the 24 preclinical studies, n = 10 recorded gamma-band activity over both cortical and subcortical areas, n = 9 studies over cortical areas and n = 5 studies included only subcortical recordings.

Effects of Ketamine on Gamma-Band Oscillations in Human EEG/MEG-studies

Ketamine was associated with an increase in gamma-band power in 8 out of 9 studies. However, mixed results emerge from the study by Li and Mashour (2019) which employed a Hidden Markov model to classify EEG signals into a discrete set of brain states which were characterized by both increase and decrease of 25-45 Hz activity.

Ketamine had an effect on both low (~ 30-60 Hz) and high gamma-band (> 60 Hz) activity in n = 4 studies (Forsyth et al. 2018; McMillan et al. 2019; Muthukumaraswamy et al. 2015; Nugent et al. 2019). In regards to the localization of gamma-band changes, n = 4 studies found that NMDA-R hypofunctioning was associated with a modulation of gamma-band activity in cortical regions (McMillan et al. 2019; Muthukumaraswamy et al. 2015; Sanacora et al. 2014; Zacharias et al. 2019), while n = 5 studies presented changes in gamma-band activity in both cortical and subcortical areas (de la Salle et al., 2016; Forsyth et al. 2018; Nugent et al. 2019; Li et al., 2019; Rivolta et al., 2015).

Connectivity analysis was conducted in n = 2 studies. A reduction in frontoparietal effective connectivity was reported by Muthukumaraswamy et al. (2015), while increased functional connectivity was reported by Rivolta et al. (2015) following subanaesthetic Ketamine administration.

Correlations between psychopathology and gamma band-activity were investigated in n = 3 studies (see Table 3). Rivolta et al. (2015) observed a negative correlation between positive symptoms and gamma-band power following Ketamine, while a negative correlation was reported by Muthukumaraswamy et al. (2015) between aberrant self-experience and parietal connectivity. No significant associations between clinical symptoms and Ketamine administration and gamma-band power were observed by de la Salle et al. (2016).

Gamma-Band Oscillations in ScZ in EEG/MEG-Recordings

Ten out of 27 ScZ studies reported an upregulation of gamma-band activity, the majority of which were in chronic ScZ-patients (n = 8). N = 7 studies reported a reduction of gamma-band activity (Kam et al., 2013; Krukow et al., 2019; 2020; Popov and Popova, 2015 ; Rutter et al., 2009; Soni et al., 2020; Strelets et al., 2006). No group difference between ScZ-patients and healthy controls was observed in n = 8 studies (Andreou et al., 2015b; Garakh et al., 2015; Hirano et al., 2015; Kissler et al., 2000; Takahashi et al., 2018; Venables et al., 2009; Zeev-Wolf et al., 2018; Lottman et al., 2019).

Mixed findings emerged from n = 2 studies, one of which reported both up- and downregulation of gamma activity (30-45 Hz) in discrete cortical regions in FEP patients (Krukow et al., 2018). Furthermore, Grent't-Jong et al. (2018) reported frequency-dependent effects (30-46 Hz and 64-90 Hz) for both FEP and chronic patents, while CHR-P participants presented gamma-band upregulation (64-90 Hz).

Out of n = 14 studies reporting connectivity results, one studies reported increased sensor-level connectivity in ScZ (Andreou et al., 2015a), n = 4 studies revealed decreased sensor-level connectivity in the ScZ group (Bandyopadhyaya et al., 2011; Kim et al., 2014; Krukow et al.,

2020; Strelets et al., 2006) and n = 6 studies reported no significant difference between ScZ and controls for gamma-band source- (Lottman et al., 2019) or sensor-level connectivity (Andreou et al., 2015b; Kam et al., 2013; ; Krukow et al., 2019; Popov and Popova, 2015; Takahashi et al., 2018). The remaining n = 3 studies reported mixed results, suggesting both increased and decreased connectivity in ScZ patients dependent on inter-regional differences (Krukow et al., 2018; Soni et al., 2020) or based on the ScZ group (FEP vs. chronic) (Di Lorenzo et al., 2015).

Fifteen out of n= 27 schizophrenia studies explored the relationship between psychopathology and gamma-band power in schizophrenia patients. Six studies (Andreou et al., 2015.a; Baradits et al., 2019; Garakh et al., 2015; Grent't-Jong et al., 2018; Kim et al., 2014; Krukow et al., 2019) identified correlations with positive symptoms, of which n = 2 studies (Garakh et al., 2015; Grent't-Jong et al., 2018) were characterized by a negative relationship (Baradits et al., 2019; Kim et al., 2014). In addition, one study reported a significant positive correlation between gamma activity and negative symptoms in chronic ScZ patients (Baradits et al., 2019). Seven studies did not find a significant association between psychopathology and gamma-band activity (Arikan et al., 2018; Bandyopadhyaya et al., 2011; Escudero et al., 2013; Kam et al., 2013; Lottman et al., 2019; Ramyead et al., 2015; Zeev-Wolf et al., 2018).

Associations between neurocognitive deficits and gamma band dysregulation in schizophrenia was investigated by Grent't-Jong et al. (2018). The authors showed a significant relationship between cognitive deficits and gamma-band power in CHR-P, FEP and chronic ScZ patients, especially in the high gamma frequency range. Moreover, Tanaka-Koshiyama et al. (2020) reported significant correlations between gamma-band activity and verbal learning.

Contrasting ScZ-studies with Different Effects on Gamma-Band Power

To identify potential sources of variability for gamma-band power findings in ScZ, we systematically compared studies that reported increases in gamma-band power (n = 11 studies) vs. those studies reporting a downregulation (n = 6 studies) as well those with no differences (n = 9) (see Table 4). One of the n = 2 studies reporting mixed results showed both increased and decreased gamma power across brain areas (Krukow et al., 2018) and was thus excluded from the present analysis. However, Grent't-Jong et al. (2018) was included as mixed results were observed in different clinical groups. Specifically, we examined differences in regard to illness stage (Chronic, FEP and CHR-P), duration of illness, medication status, recording method (EEG vs. MEG; spectral power vs. source estimates analysis), frequency range, recording design (eyes open vs. eyes closed) Overall, there were no differences between studies that reported upregulation, downregulation as well as no change between ScZ patients and controls for gamma-band power.

Discussion

The current systematic review examined the effects of NMDA-antagonists on spontaneous gamma-band activity in pre-clinical electrophysiological recordings as well as in human participants with the goal to compare these changes with alterations in EEG/MEG-data of ScZ-patients at different illness stages. Based on prior theoretical (Krystal and Anticevic, 2015; Lisman et al. 2008; Uhlhaas and Singer, 2012) and pre-clinical findings (Saunders et al. 2012), we hypothesized that NMDA-antagonists would lead to an increase in high-frequency activity as a result of a shift in E/I-balance and that these changes would be compatible with observations from ScZ-patients. Secondly, because of the role E/I-balance in shaping information transfer across large-scale networks (Shu et al. 2003; Yizhar et al. 2011), we expected that alterations in gamma-band activity would closely correlate with clinical symptoms across different stages of ScZ.

NMDA-R antagonists were associated with a consistent upregulation of both low- and high gamma-band power in both pre-clinical recordings as well as in human EEG/MEG-data across a range of cortical and sub-cortical regions. In addition, increased gamma-band connectivity was observed in the majority of preclinical studies. These findings are consistent with the widespread expression of NMDA-Rs (Zilles and Palomero-Gallagher, 2017), suggesting that NMDA-R antagonists have systemic effects across cortical and subcortical structures. Moreover, we did not observe differential effects of MK-801, Ketamine and PCP on low vs. high gamma-band frequency ranges. This observeration is in contrast with previous studies that have highlighted potential differences between low and high gamma-band oscillations in regards to generating mechanisms and laminar expression profiles (Oke et al., 2010) as well as functional correlates (Colgin et al., 2009).

Importantly, there were also no systematic differences in the effects of different NMDA-R antagonists and dosages on the pattern of gamma-band activity. Thus, Ketamine, MK-801 and PCP when administered acutely were consistently associated with increased gamma-band power while only two studies (Kittelberger, et al., 2012; Sampaio et al., 20018) examined also the effects of chronic administration. Previous studies found that chronic NMDA-R antagonists are associated with more pronounced cognitive deficits in animal models (Phillips and Silverstein, 2003). In addition, in vitro-studies showed that while acute NMDA-antagonist administration increased gamma-power, the opposite effect was observed following chronic NMDA-R hypofunctioning (McNally et al., 2013).

A central finding from the current review is that the upregulation of gamma-band power induced by NMDA-R antagonists is not consistent with the effects observed in EEG/MEG-recordings in ScZ-patients. While Ketamine administration was robustly associated with increased gamma-band power in human EEG/MEG-recordings in the large majority of studies, a similar pattern was not

observed in ScZ-patients. Thus, n = 8 studies in chronic ScZ reported upregulation of gamma-band activity, while n = 5 studies observed a decrease (Kam et al., 2013; Popov and Popova, 2015 ; Rutter et al., 2009; Soni et al., 2020; Strelets et al., 2006) and n = 5 studies no difference (Hirano et al., 2015; Kissler et al., 2000; Takahashi et al., 2018; Venables et al., 2009; Zeev-Wolf et al., 2018). Currently, studies examining resting-state gamma-band activity in FEP and CHR-P is small (FEP: n = 9 CHR-P: n = 2) but similar to findings in established ScZ, the direction of changes in gamma-band power remained inconclusive. Our results also indicate that the pattern of gamma-band activity was not moderated by medication status. Finally, connectivity analyses also revealed inconsistent patterns across studies.

Accordingly, these data indicate that the current evidence from EEG/MEG-recordings in ScZ-patients, FEP and CHR-P groups do not support a close correspondence with changes induced by NMDA-R antagonists in pre-clinical and human data consistent with the E/I-balance model of ScZ. In addition, there is only moderate evidence that alterations in resting-state gamma-band activity in clinical populations is associated with particular symptoms and/or neurocognitive deficits. One hypothesis for the generation of positive symptoms of ScZ is elevated excitability of cortical circuits (Lisman et al., 2008) that lead to the emergence of hallucinations (Jardri et al., 2016). Recent evidence from the effects of NMDA-R antagonists in healthy controls supports this view, suggesting that positive symptoms are closely correlated with the effects of Ketamine (Beck et al., 2020).

The current findings have potential implications for the E/I-balance model of ScZ as NMDA-R antagonists do not have a similar effect on gamma-band activity in pre-clinical as well as human EEG/MEG-recordings as observed in ScZ. The majority of studies that examined the correspondence between the changes induced by NMDA-R antagonists and changes in large-scale networks have been conducted with fMRI (Anticevic et al., 2015; Braun et al., 2016) and MRS

(Merritt et al. 2016). These data have provided support for the view that Ketamine-induced changes in both resting and task-related data as well as GABA and Glutamate levels resemble those observed in ScZ.

However, the current data challenge predictions of the E/I-balance model of ScZ which hypothesizes that circuit dysfunctions in ScZ, in particular during early-illness stages, are characterized by increased excitatory drive possibly due to NMDA-R hypofunctioning (Anticevic, Hu et al. 2015, Krystal and Anticevic 2015). Our systematic review suggests, that NMDA-mediated upregulation of spontaneous gamma-band activity is not consistently observed in ScZ regardless of illness-stage, suggesting that a widespread disinhibition as indexed by spontaneous gamma-band activity may not be a universal feature of circuit deficits in ScZ. Examination of gamma-band activity offers potentially complementary insights into the neurobiology of circuit functions during NMDA-R hypofunctioning and its involvement in ScZ due to the fact that the generating mechanisms of gamma-band activity have received considerable interest The important role of different classes of interneurons, in particular PV+ cells (Sohal et al., 2009), as well as the role of AMPA- and NMDA-R mediated activation of PV+ interneurons for the generation of high-frequency activity (Carlen et al., 2012; Fuchs et al. 2001) converges with evidence that E/I-balance parameters in ScZ are disrupted (Kegeles et al., 2012; Lewis et al., 2012; Pocklington et al., 2015).

The current findings raise a number of important questions that need to be addressed by future studies. Firstly, the large majority of investigation into resting-state abnormalities in ScZ have focussed on alterations in patient-populations with an established, chronic illness. Thus, it is important to provide further data on potential abnormalities in at-risk and FEP-populations .

Secondly, methodological issues need to be considered in the measurements and interpretation of fluctuations of gamma-band activity in resting-state EEG/MEG-data. High-frequency signals in electrophysiological recordings are prone to contributions from artefacts due to ocular and

muscular contributions (Hipp and Siegel, 2008). This is particular the case for measurements from spontaneous activity where the ongoing signal only contains relatively small amplitude fluctuations in the gamma-band range in contrast to stimulus-related activity. Thus, it is particularly important to employ effective artefact-correction procedures for resting-state EEG/MEG-recordings, such as ICA (Hipp and Siegel, 2008), PCA (Kaczorowska et al., 2017) and spatial filtering (Fitzgibbon et al., 2013) approaches.

Moreover, it is important to carefully characterize the pattern of high-frequency in EEG/MEG-recordings and their alterations in clinical populations. Oscillatory activity is generally characterized by a circumscribed modulation within a particular frequency which is considered to be the hallmark of a rhythmic activity. Fluctuations in EEG/MEG-recordings that do not meet this criterion are likely to be functionally and mechanistically distinct (Uhlhaas and Singer, 2012). Accordingly, it will be important to establish in future studies whether the changes induced by NMDA-R antagonists as well as in patient populations are characterized by similar spectral characteristics which is critical for the correct interpretation of the findings.

In addition, there remains a critical lack of studies on the differences and similarities between the acute and chronic effects of NMDA-R antagonists on gamma-band oscillations. While existing data points to potential differences in regard to the behavioural and circuit effects of acute vs. chronic administration (Kittelberger et al., 2012; McNally et al., 2013), further in-vivo studies are required to confirm this hypothesis.

Finally, it is important to establish differences and similarities in the consequences of NMDA-R antagonists on task-related oscillations to further test predictions of the E/I-model of ScZ. Preliminary evidence suggests that Ketamine has distinct effects on gamma-band oscillations in healthy volunteers compared to the effects observed in ScZ-patients (Grent-t'-Jong et al., 2018). However, additional variables, such as illness-stages as well as task-parameters, need to be

systematically evaluated to examine whether the pattern of high-frequency oscillations elicated by NMDA-R antagonists may be similar to those observed in ScZ.

Limitations

NMDA-R antagonists, such as Ketamine, MK-801 and PCP, impact also other neurotransmitter and receptor systems apart from NMDA-Rs which raises the question whether the effects observed on gamma-band oscillations are specifically due to hypofunction of NMDA-Rs. The current pre-clinical results, highlight, however, that regardless of the type of NMDA-R antagonists, there was a remarkable consistency in the effects of PCP, MK-801 and Ketamine on gamma-band oscillations with the large-majority of studies showing an upregulation gamma-band power and also connectivity parameters. In addition, previous research established that the upregulation of gamma-band oscillations is specifically mediated by NMDA-R 2A subunits (Kocsis et al., 2012) which are also prominently expressed on PV+ interneurons (Kinney et al., 2006) that are mechanistically involved in the generation of gamma-band oscillations (Sohal et al., 2009). Accordingly, these data highlight the possibility that NMDA-R antagonists impact on gamma-band oscillations through a specific circuit mechanism, although further research is required to substantiate this possibility.

In summary, the current systematic review highlights that NMDA-R antagonists have a unspecific frequency and topographic effect on spontaneous gamma-band activity in pre-clinical and human EEG/MEG-data. Current evidence suggests, however, that the upregulation of gamma-band power is not consistent with current findings from ScZ-patients across illness stages. Accordingly, these data call into question whether circuit modifications in the disorder are compatible with current theories implicating a shift in E/I-balance.

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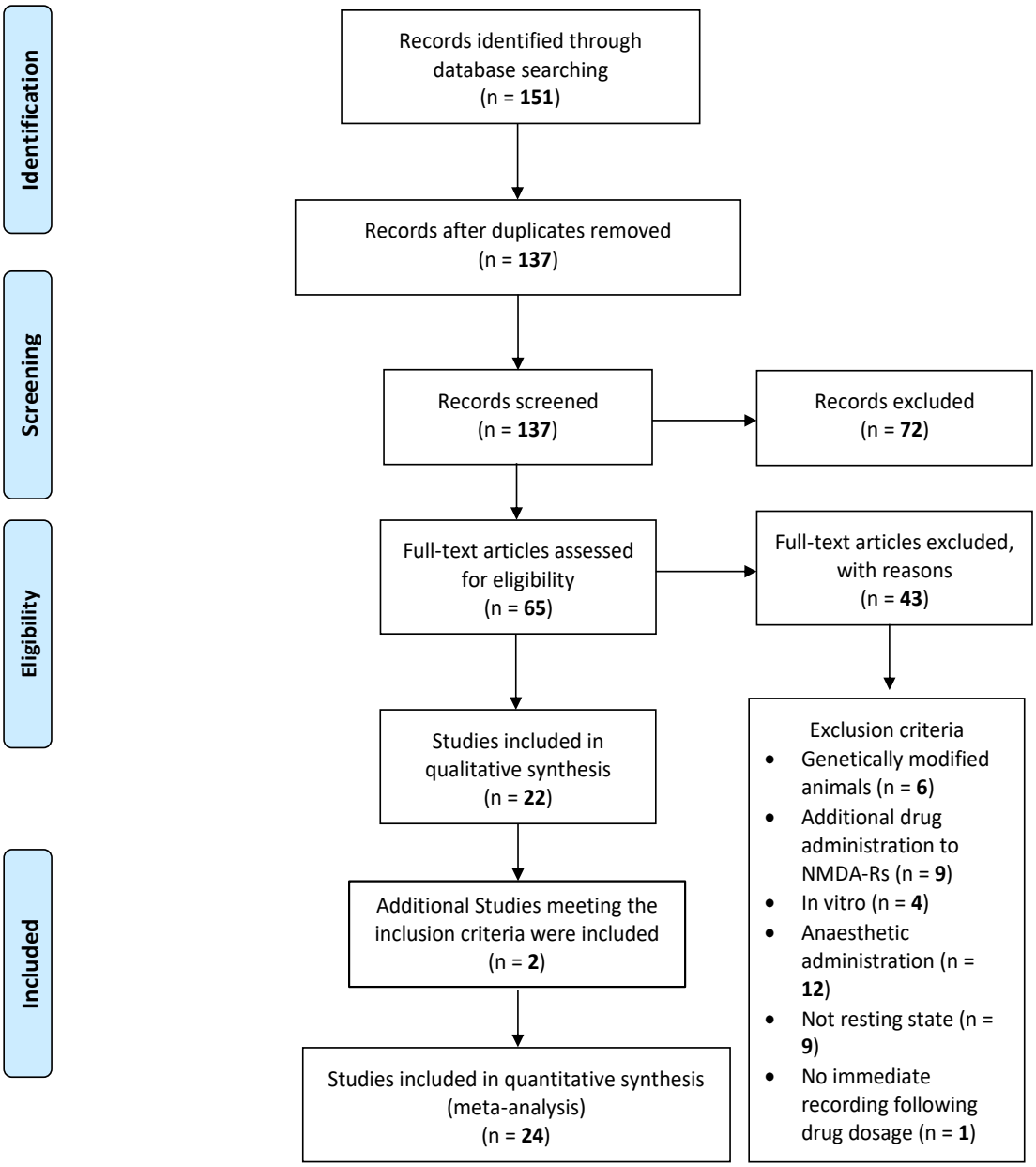

Figure 1. *PRISMA Chart of Preclinical Studies*

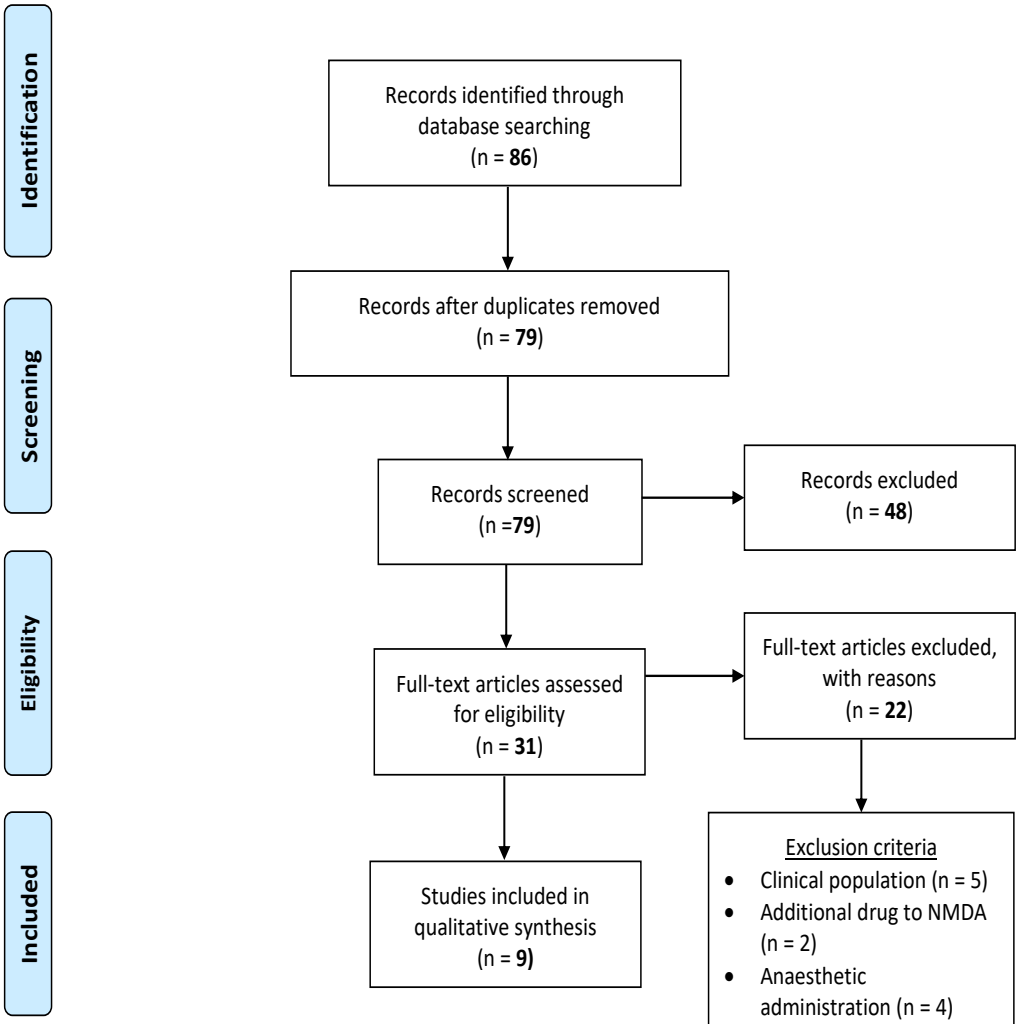

Figure 2. *PRISMA Chart of Healthy Human Studies*

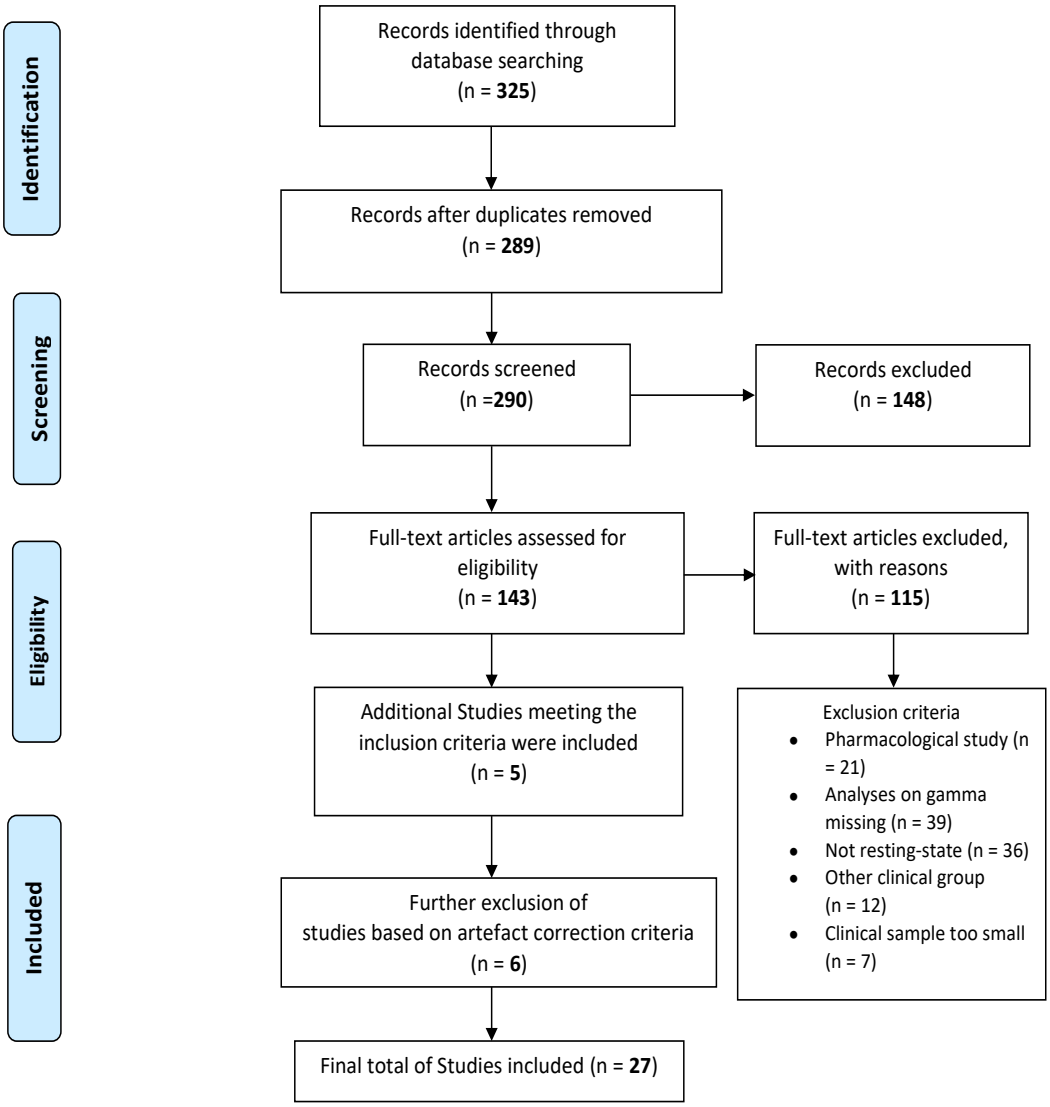

Figure. *3. PRISMA Chart of ScZ studies*

Table 1. S*ummary of Preclinical Studies*

REFERENCE	Animals	Recording/ Location	Analysis/Frequency	Pharmacology	MAIN RESULTS
Caixeta et al. (2013)	N = 8 male Wistar rats adolescent (2–3 months old)	LFP-recordings in CA1	30–100 Hz power Phase-coherence	Single Ketamine injection of 25, 50 or 75 mg/kg.	Gamma-band power and coherence increased after Ketamine administration for all three dosages.
Cordon et al. (2015)	N = 13 adult male Wistar rats	LFP-recordings in motor cortex and basal ganglia	Low (40–60 Hz) and high gamma (70–100 Hz) band power as well as coherence	Acute Ketamine (10 mg/kg)	Amplitude of high gamma (~ 80 Hz) increased following Ketamine administration in a cortico-basal ganglia network.
Hakami et al. (2009)	N = 46 adult male Wistar rats	ECoG recordings and subcortical LFP (layers V and VI; striatum)	30–80 Hz power	Acute Ketamine injection (2.5 and 5 mg/kg) MK-801 (0.08 and 0.16 mg/kg), or vehicle (0.9% NaC)	Ketamine (2.5 or 5.0 mg/kg) and MK-801 (0.08 and 0.16 mg/kg significantly increased 30-80 Hz power over cortical areas as well as in the striatum.
Hansen et al. (2018)	N = 32 adult male Wistar rats	ECoG/LFP-recordings over medial prefrontal cortex and thalamus	30–60 Hz and 60–100 Hz power estimation	Acute Ketamine (3, 10, and 30 mg/kg)	Ketamine induced a peak in the power spectrum in the low gamma-band range in all ECoG-channels for both 10 and 30 mg/kg dose of ketamine. High gamma activity was selectively enhanced by 10 and 30 mg/kg ketamine in all channels.
Hiyoshi et al. (2014)	N = 87 Sprague-Dawley rats (male,8-9 weeks old)	Cortical EEG, frontal/occipital electrodes	30-80 Hz power estimation	Acute Ketamine (2.5-30 mg/kg), PCP (1.25e10 mg/kg, MK-801 (0.05e0.2 mg/kg) (0.3e1 mg/kg)	Ketamine, PCP and MK801 exhibited an inverted U-shape dose response curve. Lower doses increased gamma-band power, while at higher doses the increase was reversed. Low PCP dosages induced spectrum changes similar to those induced by a low dose of MK-801.
Hunt et al. (2010)	N = 7 male adult rats	LFPs from left and right nucleus accumbens	29.6–90.6 Hz power analysis	Acute MK801: intra-peritoneal injection of 0.1 mg/kg and later injection of 0.5	Mk801 increased the power and frequency of gamma-band oscillations. No effects were observed at lower dosages and a reduction in gamma-band power was observed at higher dosages.

				mg/kg (3 days apart).	
Ji et al. (2013)	N =61 Black swiss adult mice.	LFPs in CA1 region	Low (30–80 Hz) and high gamma (80–150 Hz) power estimation	Acute Ketamine 50 mg/kg	Ketamine increased 30–80 Hz power while no effect was observed in the 80-150 Hz frequency range.
Jones et al. (2014)	N = 12 adult male Wistar rats.	ECoG-recordings from parietal and frontal cortex.	30–80 Hz power analysis	Acute Ketamine (5 mg/kg) and MK-801(0.16 mg/kg)	Both Ketamine and MK-801 increased 30-80 Hz power.
Kealy et al. (2017)	Adult male Wistar rats N = 15 Ketamine, MK801(n = 8 striatum, 9 hippocampus); PCP (6 striatum, 7 hippocampus).	LFP-recordings in striatum and hippocampus	30-100 Hz power	Acute Ketamine (10 mg/kg), MK-801 (0.1 mg/kg) and PCP (2.5 mg/kg)	Increased gamma power in the hippocampus following MK801, Ketamine and PCP administration. In the striatum, only PCP and MK801 administration elevated gamma-band power and HFO.
Kittelberg et al. (2012)	N = 7 (acute protocol) and n = 11 (chronic protocol) adult male Sprague-Dawley rats.	EEG implanted over frontal and parietal cortices to record hippocampal field potential (CA1 and DG).	30–50 Hz power	Single administration Ketamine (10 mg/kg), MK801 (0.2 mg/kg, n=9 s.c.); Chronic protocol: 30 mg/kg ketamine administered over 5 days.	MK801 increased gamma-band power in both CA1 and DG as well as in the frontal cortex. Gamma activity significantly decreased after chronic administration in the hippocampus.
Kocsis (2011)	N = 33 adult rats	EEG over the frontal and occipital cortices.	30-55 Hz and 65–90 Hz power	Acute Ketamine (10 mg/kg), MK801 (.2 mg/kg)	Ketamine and MK-801increased gamma-band power in both frontal and occipital cortices.
Kohtala et al. (2019)	Adult male C57BL/6JRccHsd mice	iEEG 2 electrode positioned above the fronto-parietal cortex.	Gamma low (25–40 Hz) and gamma high power (60–100 Hz)	Acute Racemic ketamine-HCl 10 mg/kg i.p.	Subanesthetic dose of ketamine (10 mg/kg, i.p.) produced a modest increase in gamma high oscillations (60–100 Hz)

Lee et al. (2017)	N = 19 male adult rats	LFP in the prefrontal cortex, dorsal hippocampus and nucleus accumbens.	30–80 Hz spectral power analysis	Acute MK801 (0, 5lg, 20lg or 50lg) infusion in one og the three areas: PFC, HIPP or NAc	Following systemic low dose of MK801 (0.16 mg/kg sc), gamma oscillations significantly increased in all regions to a similar extent as the regional infusions.
Ma and Leung (2007)	N = 26 male rats	EEG-recordings in the stratum radiatum and stratum oriens of the hippocampal CA1 region.	30-100 Hz power analysis	Acute Ketamine (6 mg/kg s.c.), MK-801 (0.5 mg/kg, i.p	Both Ketamine and MK-801 increased gamma-band power in hippocampus for the 30-70 Hz and the 70-100 Hz bands.
Molina et al. (2014)	N= 6 adult rats	LFPs in prelimbic regions of mPFC	30-90 Hz power, correlations between unit firing	Acute MK-801 (0.1–0.2 mg/kg in 0.2 ml/kg of vehicle)	Mk801 significantly increased gamma-band power in mPFC.
Nagy et al. (2016)	N = 8 Male adult Sprague–Dawley Rats.	EEG-electrodes implanted in primary auditory cortex and CA3	30-90 Hz power	Acute Ketamine (5, 10, and 80mg/kg)	Ketamine increased gamma power in A1 and CA3 which was pronounced at 80 mg/kg dose
Nicolas et al. (2011)	N = 20 adult male Wistar rats.	LFP from motor cortex and basal ganglia	30–80 Hz power, imaginary coherence analysed across the recorded structures.	Acute Ketamine (10, 25 and 50 mg/Kg)	Ketamine induced an increase in the low gamma frequencies for all doses. A ketamine-induced peak of coherent activity in the high gamma range (~80 Hz) was found.
Phillips et al. (2011)	N = 25 male adult rats.	LFP recording in frontal and occipital cortices.	40-80 Hz power	Acute injection of Ketamine, MK801 and PCP (all treatments: 1 ml/kg s.c.). crossover design (vehicle and drug-active dose)	Increased 40-80 Hz gamma power in response to all NMDA-R antagonists.

				with 7 days washout period.	
Pinault (2008)	N = 16 adult male Wistar rats	EcoG left & right frontotemporal cortices	30-100 Hz power	Single-dose Ketamine (2.5-10 mg/kg s.c.) and Mk-801 (.08-.16 mg/kg sc.) were repeated over a 2-3 day-interval period with different drug dosage.	Ketamine and MK801 led to elevated power of gamma oscillations.
Sampaio et al. (2018)	Male Adult rats	EEG electrodes recording hippocampal activity	30–50 Hz and 50–100 Hz power analysis	1) Acute Ketamine (10, 50, or 100 mg/kg) 2) Chronic administration over 10 days (once a day): group 1 –10 mg/kg, IP; group 2 –50 mg/kg, IP; group 3 –100 mg/kg, IP.	Acute administration of ketamine (10 or 50 mg/kg) increased the low gamma-band power. Acute ketamine at50-100 mg/kg increased high gamma power.
Slovik et al. (2017)	N = 4 African Green Monkeys	LFPs from primary motor cortex (M1) and external globus pallidus	30 – 48 Hz power and phase coherence	Single dose of Ketamine (10 mg/kg)	Ketamine increased gamma (30-48 Hz) power in M1 and in the external globus pallidus.
Torres et al. (2010)	N = 40 male adult rats	LFP-recording from lateral, right or left, anterior posterior to bregma.	20–50 Hz power and coherence analysis	Acute MK-801 (0.5 mg/kg i.p.)	MK801 did not cause changes in gamma-band power and coherence.
Wood et al. (2012)	N = 6 male adult rats	LFP-recordings in OFC and ACC.	30 – 55 Hz and 55–80 Hz power	Acute MK801 (0.1 mg/kg i.p.) .	MK801 increased gamma power in ACC and OFC. MK801 significantly decreased high gamma-band power correlation in ACC.

Wróbel et al. (2020)	N = 6 adult male Wistar rats	LFP in the olfactory bulb, prefrontal cortex and ventral striatum.	Low-gamma (30-60 Hz), high-gamma (70-100 Hz) and HFO (130–180□Hz)	Acute ketamine (20 mg/kg)	Ketamine was associated with bursts of HFO in the olfactory bulb, prefrontal cortex and ventral striatum

Table 2. *Summary of Studies on Healthy Volunteers.*

REFERENCE	Participants	Design	EEG/MEG-Methods	Frequency Range	Drug/Dosage	Symptom correlation	MAIN RESULTS
De la Salle (2016)	21 male volunteers (mean age=21.3). Psychopathology was evaluated with the Clinician Administered Dissociative States Scale (CADSS).	Resting state in placebo-controlled, double-blind, randomised study (minimum 5 days interval between sessions) (eyes closed).	28-channel EEG. Artefact rejection: ICA. Frequency-specific current source density (CSD) assessed at sensor-level and source-level: region of interest (ROI) approach with eLORETA.	Gamma frequency 30–60 Hz.	Racemic ketamine administered (0.26 mg/kg), followed by a constant infusion of 0.65 mg/kg.	No correlation with gamma rhythms and psychopathology.	Ketamine induced upregulation of 30-60 Hz power which was pronounced in the VMPFC, PCC ACC and anterior insula.
Forsyth et al. (2018)	30 male volunteers (mean age = 27.3).	Placebo-controlled, single-blind, three-way cross-over design. Resting state (eyes open).	64-channel EEG. Artefact rejection: ICA. Linearly constrained minimum variance (LCMV) beamforming for source reconstruction.	Low gamma (42–53 Hz), and high gamma-bands (55–67 Hz).	Racemic ketamine was administered with a 0.25 mg/kg bolus dose, followed by a0.25 mg/kg/h infusion.	N/A	EEG spectral power revealed a drug-related increase in whole-brain high gamma (55-67 Hz) and low gamma-band (42-53 Hz) power following Ketamine administration.
Li and Mashour (2019)	Fifteen volunteers (7 males, 8 females, mean	Resting state. 1st period: 5 mins of rest eyes-closed, 2nd: 40 mins	EEG 128-channel. Artefact rejection: filtering. Power spectral analysis: Hidden Markov	Gamma frequency 25–45 Hz.	Subanaesthetic dose of Ketamine (0.5 mg kg) and consequent	N/A	Modest increase in 25-45 Hz was observed following administration of sub-anesthetic Ketamine.

	age: 20–35 years).	eyes-closed with subanesthetic ketamine, 3rd : anesthetic dose, 4th: return to consciousness. .	model to classify EEG signals. EG time series was derived from frontal and posterior channels.		anesthetic dose (1.5 mg Kg).		
McMillan et al. (2019)	30 healthy males (mean age 28.2 years; SD = 6.4).	Single-blind, placebo-controlled, three-way crossover design using ketamine, midazolam and placebo. Resting state (eyes open).	EEG- 64 channels, Artefact rejection: ICA. EEG spectral changes were computed in the source space using a LCVM-beamforming approach.	Low gamma (42–53 Hz) and high gamma (55–67 Hz).	Racemic ketamine was administered as a 0.25 mg/kg bolus followed by a 0.25 mg/ kg/hr infusion.	N/A	Source power at low gamma and high gamma frequency bands increased after ketamine administration.
Muthukumaraswamy et al. (2015)	25 males (mean age: 27.2). Psychopathology examined using the 5D-ASC.	Single-blind, Placebo-controlled, randomised cross-over trials. Resting state (eyes open, supine position) recorded for 10 mins after infusion.	275-channel MEG. Artefact rejection: ICA Sensor space and source space using SAM beamformer approach. Functional connectivity-analysis at source-level was assesse on bilateral paretal, motor and occipital	Low gamma (30 – 49 Hz), and high gamma (51–99 Hz).	Ketamine infusion 0.25 mg/kg delivered over1 m, then of 0.375 mg/k infusion.	Participants' self-report of blissful state and decrease in parietal gain. Modulation in NMDA-mediated backward connectivity.	Increases in source power were seen in gamma-band following ketamine administration. These oscillatory changes were accompanied by temporally sustained reductions in frontoparietal effective connectivity.

			networks (altered by ketamine).				
Nugent et al. (2019)	26 healthy participants (mean age: 33.9). Psychopathology was assessed with the CADSS, BPRS and Young Mania scale.	Double-blind, placebo-controlled, randomised cross-over study. Resting state obtained at baseline at 6–9 h post-ketamine/ post-placebo infusion, and at 11–13 days post-infusion. Eyes closed	275-channel MEG-system. Artefact rejection: filtering. Source localisation using SAM Beamformer weights.	Gamma frequencies 30–50 Hz and 50- 100 Hz.	Single Ketamine infusion 0.5 mg/kg.	N/A	Increased gamma power following ketamine infusion was observed in widespread cortical and subcortical areas.
Rivolta et al. (2015)	12 participants (mean age: 29.6 years). Positive and Negative Syndrome Scale (PANSS).	single-blind, randomized, placebo-controlled, crossover design. Resting state, eyes closed and visual.	275 sensor MEG-system. Artefact rejection: automatic artefact rejection. Sensor-level power analysis and DICS analysis of sources. Connectivity at source-level was estimated using a transfer entropy measure.	Gamma frequency30 –90 Hz.	Initial dose of S-ketamine 10 mg or NaCl 10 ml, followed by a continuous intravenous infusion of 0.006 mg/kg of ketamine or saline (placebo condition).	Negative correlation between post-ketamine gamma band power in right hippocampus and PANSS positive scale.	Ketamine increased gamma-power in subcortical and cortical regions. Moreover, increased information transfer in a thalamo-cortical network after ketamine was observed.
Sanacora et al. (2014)	32 Males (age range: 30–45 years), 17 receiving	double-blind, placebo-control, randomized	28-channel EEG, spectral power, source localisation.	Gamma frequency 32.5 to 48Hz.	Single administration of Ketamine 0.5 mg/kg (i.v.), 60	N/A	Increases 32.5-48 Hz power after Ketamine were observed which correlated with total CADSS scores.

	ketamine and 15 placebo. Psychopathology evaluated with CADSS and MADRS.	study. Resting state.			minutes infusion.		
Zacharias et al. (2019)	24 (17 with complete dataset) healthy male volunteers (mean age: 27.5). Psychopathology evaluation: N/A.	Resting state eyes closed Placebo-controlled, randomized, cross-over study. .	32-channel EEG. Artefact rejection: ICA. Sensor power FFTp (fast Fourier transformation band power) analysis.	Gamma frequencies 30–50 Hz.	S-ketamine (0.1 mg/kg) initial bolus, 0.015625 mg-1 constant infusion with reduction of 10% of dose every 10 mins (max 1 h)	N/A	Increased gamma-band power over frontal and right parietal electrodes following Ketamine administration.

Table 3. *Summary of Included Clinical studies*

REFERENCE	Participants	Design	Recording/Location/	Frequency range	Symptom correlation	MAIN RESULTS
Andreou et al. (2015a)	22 FEP ScZ patients (mean age: 24.09 years, medicated) and 22 unmedicated controls. Psychopathology measures: PANSS	Resting state, eyes closed.	64-channel EEG: Source-level analysis; Power envelope correlation.	Gamma frequency 40 Hz.	For Disorganised and positive symptoms: Patients with low symptoms and higher mean connectivity Compared to controls and high-symptom patients	Increased connectivity in ScZ patients in a network involving left inferior frontal/orbitofrontal, lateral and medial temporal, and inferior parietal areas. Gamma-band connectivity was higher in patients with low positive and disorganization symptom levels.
Andreou et al. (2015b)	28 UHR-individuals, 18 (medicated) FEP-patients, 23 controls. Psychopathology measures: PANSS.	Resting state, eyes closed	64-channel EEG: sensor and source power; source connectivity.	Gamma frequency 40 Hz.	N/A	No differences in gamma-band connectivity.
Arikan et al., (2018)	23 (20 males) paranoid ScZ-patients (medication free, mean age: 39), 11 controls (5 males, mean age: 37.5 years). Psychopathology measure: SANS and SAPS scales	Resting state, eyes closed.	19-channel EEG: spectral power.	Gamma Frequency 30-50 Hz.	Correlation between positive and negative symptoms, and beta-gamma power did not reach significance	Higher 30-50 Hz power over central electrodes C3 and a trend for higher gamma-band power over Cz in patients compared to controls.
Bandyopadhyaya et al. (2011)	20 male chronic ScZ-patients (age mean: 28.56 years); 20 male first-degree relatives (age mean: 33.97 years), 20 male controls (age mean: 28.8 years). All drug	Resting state, eyes closed.	128-Channel EEG: Spectral power, coherence.	Gamma Frequency 30-100 Hz	No relationship between scores of positive symptoms, negative symptoms, general psychopathology, paranoid belligerence and gamma power	Increased 30-100 Hz power over central, left and right temporal and right frontal areas in ScZ patients. Lower gamma-band coherence in ScZ patients.

	naïve. Psychopathology measures: PANSS					
Baradits et (al. (2019)	60 chronic ScZ (mean age = 35.2 years, medicated), control 76 (unmedicated, mean age = 32.3). Psychopathology measures: PANSS	Resting state, eyes closed.	256-channel EEG: sensor-level spectral power.	Gamma Frequency 31-48 Hz	Relationship between Higher symptom severity (PANSS total score, negative and hostility factor) and increased gamma power in the left occipital cortex	Higher gamma-band power in ScZ patients over fronto-central and posterior clusters that correlated with .Increase in gamma with symptom symptom severity.
Di Lorenzo et al., (2015)	77 ScZ-patients (25 FEP, 52 chronic), 78 Controls (age matched). Medicated. Psychopathology measures: PANSS Cognitive measure: Cognition Rating Scale (SCoRS)	Resting state, eyes closed.	37-channel EEG: Source Functional Connectivity (lagged phase synchronization).	Gamma Frequency 30-80 Hz	N/A	Higher connectivity between right occipital-prefrontal and parieto-temporal ROIs in ScZ. Gamma-band connectivity: increased in FEP; both decrease and increase (region-dependent) in chronic patients.
Escudero et al. (2013)	15 chronic, medicated ScZ-patients (age mean; 31.93, medicated), control:17 (age mean: 32.29, unmedicated). Psychopathology measures: SAPS.	Resting state, eyes closed.	148-channel MEG: sensor power spectral density.	Gamma Frequency 30-40 Hz.	No significant correlation between spectral features and clinical variables.	Increased 30-40 Hz power in in central regions in ScZ patients.
Garakh et al. (2015)	32 FEP Schizophrenia patients (age mean: 28.9 years, mostly medicated) 32 schizoaffective disorder (age mean: 27.6 years) and 40 controls. Psychopathology measures: PANSS	Resting state, eyes closed.	19-channel EEG: Sensor-analysis of 30-40 Hz power.	Gamma frequency 30-40Hz.	In the schizoaffective group PANSS positive subscale scores negatively correlated with gamma-band power in Fp1 electrode	No group differences in gamma-band power between ScZ, Schizoaffective and controls.

Grent't-Jong et al. (2018)	88 CHR-P individuals; 21 FEP (medication naïve) n; 34 chronic schizophrenia Psychopathology measure: PANSS.	Resting state, eyes open.	248-channel MEG: whole brain source power analysis (FFT). Granger causality connectivity across 18 nodes.	Low gamma (LGF) (30-46 Hz), high gamma (HGF) (64-90 Hz)	PANSS P3: negative correlation with gamma power (FEP). CHR-P: negative correlation between BACS scores and gamma à increase in gamma-band activity was related to neurocognitive deficits. FEP: opposite relationship. Chronic: BACS scores correlated with a reduction of gamma-band power.	CHR-P showed increased high-gamma power. For FEPs, increased occipital and decreased PFC activity at low-gamma power was observed, while posterior and decrease frontal at high-gamma power were increased. Chronic ScZ patients showed decreased low and high gamma-band activity.
Hirano et al. (2015)	18 chronic ScZ patients (mean age: 45.4, medicated) 18 matched controls (mean age:44.1, unmedicated). Psychopathology measure: SANS, SAPS.	Resting state, eyes closed.	71-channel EEG: sensor estimates of spectral power.	Gamma Frequency 30-100Hz.	The left hemisphere tangential and radial dipole-induced gamma power during the 40-Hz stimulation were positively correlated with auditory hallucinations. No other significant correlation.	No group difference in gamma power.
Kam et al. (2013)	132 Chronic ScZ (age: 40, mostly medicated); 76 bipolar disorder (age mean=41, medicated), 136 controls (mean age =39, unmedicated). Psychopathology measures: PANSS	Resting state, eyes closed.	32-channel EEG: CSD estimates, spectral power. Interhemispheric coherence	Gamma Frequency 30-50 Hz	Gamma showed no significant effects of Diagnosis	Decreased 30-50 Hz power in ScZ patients compared to bipolar-disorder patients.
Kim et al. (2014)	20 Chronic ScZ Patients, medicated (mean age: 22.8 years), 20 controls (mean age 22.1 years)	Resting state, eyes open.	Whole-head 306-channel MEG: spectral power, coherence.	Gamma Frequency 30–50 Hz.	Significant correlation ($p < 0.05$) between the positive syndrome scale and the DMN activity of	Higher 40 Hz power in left posterior cingulate cortex in ScZ patients. However, coherence of 40 Hz activity was reduced.

	Psychopathology measure: PANSS.				gamma power in the MPFC but not in PCC.	
Kissler et al. (2000)	15 chronic ScZ patients (mean age 30.2 years, medicated) and 15 healthy controls (mean age 35.8 years. Psychopathology measure: PANSS, SANS.	Resting state, eyes open.	148-channel MEG: sensor spectral power.	Gamma frequencies: 30-45 Hz 46-6Hz, 61-71 Hz.	N/A	No differences in gamma-band power.
Krukow et al. (2018)	32 FEP patients (all on antipsychotic medication), 35 controls. Psychopathology measure: PANSS.	Resting state, eyes closed	21-channel EEG: Connectivity measures: phase lag index (PLI) for each frequency band.	Gamma frequency 30-45Hz.	N/A	Lower PLI-values were observed between fronto-central electrodes, but higher for temporo-parietal connections.
Krukow et al. (2019)	35 FEP-patients (mostly medicated, mean age 21.30 yrs) 35 healthy controls (mean age 21.54 yrs). Psychopathology measure: PANSS.	Resting state, eyes closed	21-channel EEG: Connectivity: PLI. Minimum spanning tree metrics based on PLI matrix computed for each frequency band.	Gamma frequency 30–48 Hz.	Positive relationship between positive symptoms and gamma PLI connectivity	No between-group differences in PLI-values between ScZ and controls were observed at gamma-band frequencies but reduced network efficiency.
Krukow et al. (2020)	34 FEP patients (medicated), 30 controls. Psychopathology measure: PANSS.	Resting state, eyes closed.	21-channel EEG, Artefact rejection: filtering. Source localization and functional connectivity analysis.	Gamma Frequency: 30-45 Hz	N/A	ScZ patients were characterized reduced gamma band-power in the Inferior Parietal Lobule, Middle Frontal Gyrus and Postcentral Gyrus compared to healthy controls.
Lottman et al. (2019)	19 FEP-patients (medicated); 24 controls Psychopathology measure BPRS, SANS, SAPS and RBANS (cognitive functioning assessment).	Resting-state eyes closed.	148-channel MEG: source-power estimation. Artefact rejection: ICA. Functional connectivity pairwise	Gamma Frequency 30-50 Hz.	No significant relationship between patient symptom scores and gamma band connectivity	No significant group differences in gamma-band power.

			Pearson correlation between RSN time courses.			
Popov and Popova (2015)	57 Chronic ScZ (mean age: 37.05, medicated) controls 28 (age mean: 29.32). Psychopathology measure: PANSS.	Resting state, eyes open.	148-channel MEG: sensor spectral power, cross-frequency coupling analysis.	Gamma Frequency 40-100 Hz.	N/A	Reduced 40-100 Hz power in ScZ patients in posterior and frontal brain regions.
Ramyead et al. (2015)	63 CHR-P (23 transitioned to psychosis-CHR+)	Resting state, eyes open.	19-channel EEG: current source localizations density (CSD); lagged phase synchronization.	Gamma Frequency 30-50 Hz.	No symptom correlation with gamma band frequency. CHR+ gamma activity was positively correlated with cognitive performance	Increased gamma-band activity in mPFC for CHR+ who transitioned to psychosis (n = 23) compared to healthy controls.
Rutter et al. (2009)	38 chronic ScZ Patients (mean age: 31.2; mostly medicated) and 38 controls (mean age: 32.5).	Resting state, eyes closed.	275-channel MEG: sensor and source power analysis.	Low gamma (30-80 Hz), High gamma (80-150 Hz).	N/A	ScZ-patients showed reduced 30-80 Hz and 80-150 Hz power in the posterior region of the medial parietal cortex compared to controls.
Schulz et al. (2017)	17 paranoid ScZ Patients (mean age: 37.5; depot antipsychotic medication), 21 healthy controls (mean age: 36.7).	Resting state, eyes closed.	64-channel EEG: sensor-level spectral power, phase synchronisation. Artefacts visually inspected.	Gamma Frequency 25-60 Hz	N/A	Increased phase-locking power of 25-60 Hz in ScZ patients compared to controls.
Soni et al. (2020)	32 chronic ScZ patients (medicated), 28 first-degree relatives, 31	Resting state, eyes closed.	128-channel EEG: Artefact rejection: ICA.	Gamma Frequency: 30.1–100 Hz	N/A	Patients with schizophrenia showed significantly lower power spectral density in the gamma band in the left

	controls. Psychopathology measure: SANS, SAPS.		Power spectral source estimates and connectivity analysis			parahippocampal gyrus and reduced functional connectivity compared.
Strelets et al. (2006)	20 ScZ patients: FEP n=10 (no neuroleptic medication, age mean: 25 years), n=10 chronic (age mean: 33); controls: 38 (age mean: 28). Psychopathology measures: PANSS	Resting state, eyes closed.	16-channels EEG: spectral power, phase synchronization and coherence.	Gamma Frequency 20-40 Hz	N/A	Lower gamma-band power in parietal and occipital areas in ScZ-patients and reduced coherence. FEP patients showed no significant inter-hemisphere coherence interactions at gamma-band frequencies.
Takahashi et al. (2018)	21 Chronic ScZ patients (drug naïve, mean age: 28.1) 31 controls (mean age27.9). Psychopathology measure: Brief Psychiatric Rating Scale (BPRS)	Resting state, eyes closed.	16-channel EEG: sensor analysis of spectral power and functional connectivity (phase lag index).	Gamma Frequency 30-60 Hz,	N/A	No group differences in 30-60 z spectral power; lower gamma-band connectivity ScZ
Tanaka-Koshiyama et al. (2020)	157 chronic ScZ patients (medicated), 145 controls. Psychopathology measure: SANS, SAPS Neuropsychological measures:	Resting state, eyes open.	38-channel EEG, artefact rejection: PCA. Power spectral analysis.	Gamma Frequency: 30-50 Hz.	Gamma band was negatively correlated with negatively correlated with verbal learning (CVLT scores) in ScZ at Fp2, verbal learning ability was positively correlated with gamma at F4 and T8.	Patients with schizophrenia showed significantly higher gamma-band power.
Venables et al. (2009)	43 chronic ScZ Patients (mean age: 44.8, medicated); 79 controls (mean age: 43.7); n=61 first-degree relatives of ScZ (mean age: 50).	Resting state, eyes closed and eyes open.	27-channel EEG: Sensor analysis of spectral power amplitude measure.	Gamma Frequency 30-50Hz.	N/A	No group differences in 30-50 Hz power.

	Psychopathology measure: Diagnostic Interview for Genetic Studies (DIGS)					
Zeev-Wolf et al. (2018)	39 chronic ScZ patients (medicated), 25 controls. Psychopathology measure: PANSS.	Resting-state, eyes-open	248-channel MEG: Artefact rejection: ICA. Source localisation.	Gamma Frequency 31-70 Hz.	No significant correlation between brain activity and positive or negative symptom scores	No significant group differences in gamma-band power between ScZ-patients and controls.

Table 4. *ScZ studies with different effects on gamma activity*

Parameter	Studies with gamma upregulation *	Studies with gamma downregulation	Studies with no group differences in gamma-band *	Statistics
Count	11	7	9	N = 27 (100%); p = 0.678
Clinical subgroup (some overlap)	Chronic: 8 studies, FEP: 2 studies, CHR-P: 2 studies.	Chronic: 5 studies, FEP: 3 study.	Chronic: 6 studies, FEP: 4 studies, CHR-P: 1 study.	N = 31 (100%); p = 0. 501
Recording method	8 EEG, 3 MEG.	5 EEG, 2 MEG.	5 EEG, 4 MEG.	N = 27 (100%); p = 0. 678

Eyes open/closed (some overlap)	Eyes open: 4, eyes closed: 8.	Eyes open: 1, eyes closed: 6.	Eyes open: 3, eyes closed: 6.	N = 28 (100%); *p* = 0. 755
Sensor-level spectral power vs source estimates	4 source power analysis; 7 sensor analysis.	3 source power analysis; 5 sensor analysis	4 source-power estimation; 6 sensor analysis.	N = 29 (100); *p* = 1.00
Low (<60) vs. high (>60) gamma (some overlap)	Low gamma: 11, high gamma: 3.	Low gamma: 7, high gamma: 3.	Low gamma: 9, high gamma: 4.	N = 37 (100%); *p* = 0.809
Duration of illness in chronic patients (years)	7.40 (4.98)	13.03 (11.58) (3 studies)	6.46 (9.77)	H(2) = 1.36; *p* = .506
% of male patients	69.59%	57.76%	73.3%	H(2) = 3.76, *p* = .152
Mean age of participants (SD)	31.75(7.74)	30.69(6.3)	32.99(8.29)	H(2) = 3.836; *p* = .147
Artefact correction method	ICA: 5 Filtering: 5 PCA: 1	ICA: 2 Filtering: 4 Filtration and factor analysis: 1	ICA: 5 Filtering: 2 PCA: 2	N = 27 (100%); *p* = .4223
Medication status	Unmedicated: 3 Medicated: 8	Unmedicated: 1 Medicated: 5	Unmedicated: 3 Medicated: 6	N = 26 (100%); *p* = 0.865
Nr of studies reporting sensor-level vs. source-level connectivity	Sensor-level: 2 Source-level: 3	Sensor-level: 3	Source-level: 4 Sensor: 1	N =13 (100%); *p* = 0.155

*** Grent-‘t-Jong et al. (2018) subdivided into two groups counting as two separate studies: CHR-P results (upregulation effect category) and FEP + Chronic (upregulation effect category).**