Ketamine Modulates Theta and Gamma Oscillations

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Abstract

■ Ketamine, an *N*-methyl-D-aspartate (NMDA) receptor glutamatergic antagonist, has been studied as a model of schizophrenia when applied in subanesthetic doses. In EEG studies, ketamine affects sensory gating and alters the oscillatory characteristics of neuronal signals in a complex manner. We investigated the effects of ketamine on in vivo recordings from the CA3 region of mouse hippocampus referenced to the ipsilateral frontal sinus using a paired-click auditory gating paradigm. One issue of particular interest was elucidating the effect of ketamine on background network activity, poststimulus evoked and induced activity. We find that ketamine attenuates the theta frequency band in both background activity and in poststimulus evoked activity. Ketamine also disrupts a late, poststimulus theta power reduction seen in control recordings. In the gamma frequency range, ketamine enhances both background and evoked power, but decreases relative induced power. These findings support a role for NMDA receptors in mediating the balance between theta and gamma responses to sensory stimuli, with possible implications for dysfunction in schizophrenia. ■

INTRODUCTION

Two main hypotheses for the pathogenesis of schizophrenia focus on disorders of dopamine (Abi-Dargham et al., 2002; Carlsson, Waters, Waters, & Carlsson, 2000; Akil et al., 1999; Weinberger, Berman, & Illowsky, 1988) and glutamate mechanisms (Coyle, 2006; Tamminga, 1998). Many of the changes in the glutamatergic dysfunction model are reported in hippocampus (Reynolds & Harte, 2007). Ketamine is a glutamate-receptor blocking agent that can mimic several symptoms and cognitive deficits associated with schizophrenia (Lahti, Weiler, Tamara Michaelidis, Parwani, & Tamminga, 2001). Ketamine models both the hyperdopaminergic and hypoglutamatergic putative mechanisms of schizophrenia (Gunduz-Bruce, 2009). Acute administration of ketamine is accepted as a model of psychosis and is correlated with both positive and negative symptoms of schizophrenia in both humans (Adler et al., 1999) and animals (Adams & Moghaddam, 1998). At pharmacologically relevant concentrations, ketamine acts as a noncompetitive antagonist of the *N*-methyl-D-aspartate (NMDA) receptor. This mechanism is considered responsible for the schizophrenia-like symptoms (Tsai & Coyle, 2002) and is linked to the disinhibition of hippocampal interneurons (Lewis & Moghaddam, 2006; Greene, 2001). Enhancement of NMDA receptor action is implicated in reducing some of the positive symptoms of schizophrenia (Wood, 2005), suggesting that facilitating NMDAR function may be a useful therapeutic target.

Ketamine at subanesthetic doses has been extensively studied as a model of glutamatergic dysfunction in animal models of schizophrenia (Bubenikova-Valesova, Horacek, Vrajova, & Hoschl, 2008; Becker et al., 2003; Moghaddam & Jackson, 2003; Mansbach & Geyer, 1991). Loss of glutamate receptor function is believed to underlie a range of cognitive and sensory deficits associated with the disease (Coyle, 2006). Ketamine has been shown to alter both glutamatergic and dopaminergic neurotransmission, in brain regions including neocortex, entorhinal cortex, hippocampus, medial septum, thalamus, and brain stem among others (Becker et al., 2003). Specifically interesting are the effects that ketamine has on gamma oscillations, as they are thought to be crucial for binding together different features of incoming sensory information (Gray & Singer, 1989) as well as coordinating the activity of local neuronal populations (Lee, Williams, Haig, & Gordon, 2003). Gamma oscillations have also been linked to information processing (Gray & Singer, 1989), consciousness (Engel, Fries, & Singer, 2001), attention (Vidal, Chaumon, O'Regan, & Tallon-Baudry, 2006; Herrmann, Munk, & Engel, 2004; Tiitinen et al., 1993), and memory (Kaiser & Lutzenberger, 2005; Howard et al., 2003; Sederberg, Kahana, Howard, Donner, & Madsen, 2003; Tallon-Baudry, Bertrand, Peronnet, & Pernier, 1998). Induced gamma oscillations are implicated in object representation (Rodriguez et al., 1999; Tallon-Baudry, Kreiter, & Bertrand, 1999) and activation of associative memories (Miltner, Braun, Arnold, Witte, & Taub, 1999; Pulvermuller, Lutzenberger, & Preissl, 1999). Stimulus evoked gamma-band responses have been suggested to reflect synchronously active neural assemblies and the precise temporal relationship of concurrently incoming stimuli (Tallon-Baudry et al., 1999). Recently, it was shown that the power of gamma oscillations correlates with working memory during the *n*-back task in humans (Sederberg et al., 2006; Howard

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et al., 2003). In patients with schizophrenia, this correlation is disturbed (Cho, Konecky, & Carter, 2006). A recent clinical paper has shown that increasing gamma oscillations with a novel GABA type A agonist correlates with increased cognitive performance in schizophrenic patients (Lewis et al., 2008). Several studies have demonstrated increased gamma power after ketamine administration in hippocampus in vivo (Hinman, Sabolek, & Chrobak, 2007; Ma & Leung, 2007). Because ketamine acts through blocking glutamatergic receptors and has an inhibitory effect on cells, it is perhaps unexpected to see an increase of gamma power. However, in hippocampus, NMDA receptors are located not only on pyramidal cells but also on several classes of interneurons such as oriens lacunosum-moleculare (O-LM) cells (Nyiri, Stephenson, Freund, & Somogyi, 2003; Hajos, Freund, & Mody, 2002) or bistratified and basket cells (Buhl, Szilagyi, Halasy, & Somogyi, 1996; Koh, Geiger, Jonas, & Sakmann, 1995; McBain & Dingledine, 1993), suggesting that ketamine may be acting to increase gamma power via disinhibition.

Theta oscillations have been implicated in sensorimotor integration (Bland & Oddie, 2001; O'Keefe & Recce, 1993), emotion (Gray, 1982), and formation and recall of episodic and declarative memory (Jacobs, Hwang, Curran, & Kahana, 2006; Vertes, 2005), as well as working and long-term memory encoding (Klimesch, Freunberger, Sauseng, & Gruber, 2008). It was suggested that restoring theta-range rhythmicity restores hippocampal function (McNaughton, Ruan, & Woodnorth, 2006). The theta rhythm may also play a role in information processing using an attentional double-gating mechanism, "filtering-in" signals for effective registration and encoding of selected information and additionally "filtering-out" interfering inputs (Vinogradova, 1995). A relationship between gamma and theta oscillations has been well established in hippocampus (Canolty et al., 2006; Bragin et al., 1995).

In this article, we analyze data acquired in an auditory paired-click gating paradigm. This experimental design has been extensively investigated in normal cognitive and schizophrenic studies (Brockhaus-Dumke, Mueller, Faigle, & Klosterkoetter, 2008). In this auditory gating paradigm in healthy subjects and animals, the ratio of EEG responses of the second click to the first click is significantly less than one, what is called "sensory gating." In patients diagnosed with schizophrenia, this sensory gating phenomenon is reduced or abolished (the ratio is close to one). Several studies suggest that gating ratio abnormalities in schizophrenia are actually mediated by reductions in the first click response in unmedicated patients, rather than increased amplitude of the second (Clementz & Blumenfeld, 2001; Jin et al., 1997; Jin & Potkin, 1996; Adler, Rose, & Freedman, 1986; Freedman, Adler, Waldo, Pachtman, & Franks, 1983).

Previous studies from our group and others demonstrate a high degree of similarity between human and mouse EEG and ERPs for morphology, as well as physiological and pharmacological response properties using this configuration (Ehrlichman, Maxwell, Majumdar, & Siegel, 2008; Halene & Siegel, 2008; Rabin et al., 2008; Metzger, Maxwell, Liang, & Siegel, 2007; Phillips, Ehrlichman, & Siegel, 2007; Maxwell, Ehrlichman, Liang, Gettes, et al., 2006; Maxwell, Ehrlichman, Liang, Trief, et al., 2006; Maxwell, Liang, et al., 2006; Siegel et al., 2003, 2005; Connolly et al., 2003, 2004; Maxwell, Kanes, Abel, & Siegel, 2004; Maxwell, Liang, et al., 2004; Umbricht et al., 2004; Umbricht, Latanov, Vissotksi, Nitsch, & Lipp, 2002; Stevens, Kem, & Freedman, 1999; Stevens, Kem, Mahnir, & Freedman, 1998; Stevens & Wear, 1997; Stevens et al., 1996; Stevens, Meltzer, & Rose, 1995). In animals, acute injection of ketamine similarly affects this ratio, as well as the magnitude and latency of the ERP components (Ehrlichman et al., 2008; Maxwell, Ehrlichman, Liang, Trief, et al., 2006; Connolly et al., 2003, 2004). As such, ketamine may represent a model of altered circuitry in schizophrenia. We use the auditory paired-click paradigm to elucidate the contributions of background, evoked, and induced power changes whose interaction obscure the role of altered glutamatergic responses following ketamine (using 5 vs. 20 mg/kg) application.

METHODS

Animals

C57BL/6Hsd (B6) male mice (n = 20) were obtained at 8 weeks of age from Harlan (Indianapolis, IN). All protocols were performed in accordance with University Laboratory Animal Resources guidelines and were approved by the Institutional Animal Care and Use Committee. Testing was conducted between 10 and 13 weeks of age. Mice were housed three to four per cage in a light- and temperature-controlled Association for Assessment and Accreditation of Laboratory Animal Care-accredited animal facility. All efforts were made to minimize animal number and suffering. Water and standard rodent chow were available ad lib. Experiments were conducted during the light phase between the hours of 0900 and 1300. Mice were acclimated to the housing facility for at least 1 week prior to all procedures.

Treatment

Treatment groups consisted of acute ketamine (5 and 20 mg/kg ip). In the ketamine condition, 20 mg/kg ip was used, unless otherwise stated. Although the ketamine doses used in this study represent 5% and 20% of the minimum anesthetic dose, we assessed their effects on locomotor activity to control for possible motor effects on EEG. Mice (n = 6/group, total = 18) were tested in the same home cage environment for the same duration as recording of ERPs according to previously published methods (Halene & Siegel, 2008). Animals were transferred from their housing facility to the locomotor activity testing room in their home cages for a habituation period of 15 min prior to testing. Animals were placed in automated locomotor activity frames that creates a grid of infrared light beams throughout the transparent home cages (31 cm length, 19 cm width, 16 cm height) (Med Associates,

St. Albans, VT, USA). Data were collected over a total period of 30 min using a personal computer.

Surgery

Animals underwent stereotaxic implantation of electrode assemblies (PlasticsOne, Roanoke, VA) for nonanesthetized recording of auditory ERPs as previously reported (Maxwell, Ehrlichman, Liang, Trief, et al., 2006; Connolly et al., 2003, 2004; Maxwell, Kanes, et al., 2004; Siegel et al., 2003). Animals were anesthetized with isoflurane, and unipolar recording electrodes were placed in the CA3 hippocampal region (positive polarity) (1.4 mm posterior, 2.65 mm lateral, and 2.75 mm deep relative to bregma) and referenced to the ipsilateral frontal sinus (negative polarity) to reflect whole-brain electrical activity. Electrode localization in CA3 was histologically verified using the Perl's iron method as previously described (Figure 1A; Connolly et al., 2003; LaBossiere & Glickstein, 1976). ERPs recorded from this electrode configuration are characteristically similar to human recordings from the Cz scalp location as illustrated in the third figure from a prior publication (Siegel et al., 2003). The electrode pedestal was secured to the skull using dental cement and cyanoacrylate glue. EEGs were recorded 2 weeks after electrode surgery, as described below.

Recording

EEGs were recorded during the presentation of a paired-click auditory task. All raw EEG was inline band-pass filtered between 1 and 500 Hz during collection. Stimuli were generated by Micro1401 hardware and Spike 5 software (Cambridge Electronic Design, Cambridge, UK) and were delivered through speakers attached to the cage top. All recordings were performed in a home cage environment that was placed in a Faraday cage 15 min before stimulus onset. A series of 50 pairs of white noise clicks (10 msec in duration each) with a 500-msec interstimulus interval were presented with a 9-sec intertrial interval at 85 dB compared with background of 70 dB. Testing commenced 5 min after intraperitoneal injection for each treatment group.

Data Analysis

Data analysis was performed using MatLab (MathWorks, Natick, MA) and JMP (SAS, Cary, NC) software. Four mice were rejected from the study because of severe recording artifacts. Two groups of eight mice were each analyzed under two conditions: after saline and after ketamine injection using a within-subjects experimental design. The first group was injected with 5 mg/kg ketamine and the second with 20 mg/kg ketamine. Single-trial epochs between −2.5 and 2.5 sec relative to the first click were extracted from the continuous data. Individual sweeps were rejected for movement artifact on the basis of a criterion of two times the root-mean-squared amplitude per mouse. The mean number of trials in each condition was not significantly

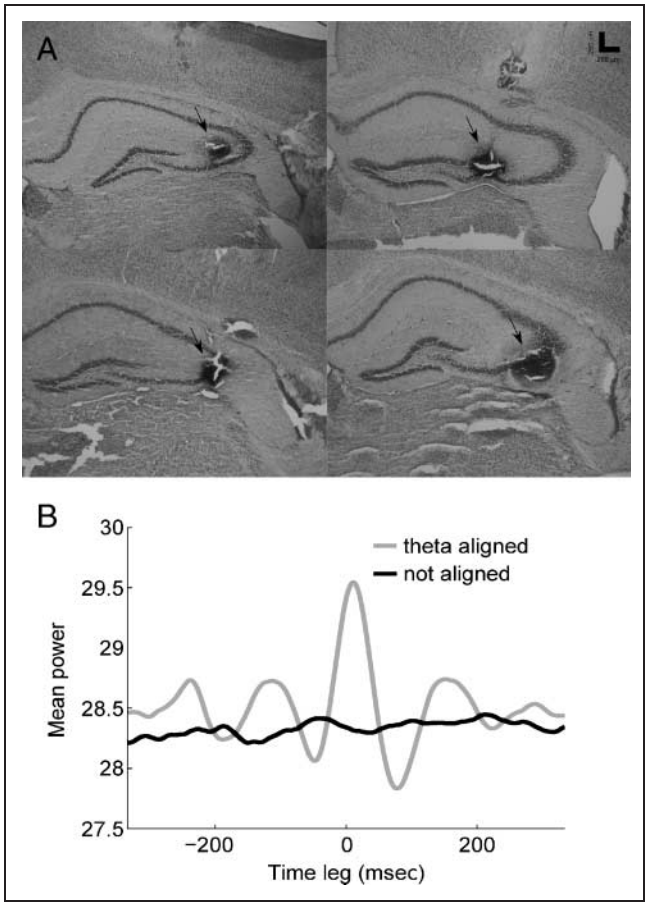

Figure 1. Demonstration of electrode placement in hippocampus. (A) Positive electrode tips are marked using Perl's iron reaction. Four examples are shown with the characteristic staining for iron adjacent to CA3. (B) Gamma power is modulated by theta oscillation phase. The gray line represents a grand average of gamma power (30–50 Hz) aligned to the peak of the theta power (3–12 Hz). The black line shows gamma activity that is not aligned to the theta oscillations. The peak of the gamma is shifted 10 msec from the peak of the theta with secondary peak locations compatible with 7–8 Hz oscillations.

different. ERPs for the first and the second clicks were obtained by averaging epochs centered at Time 0 and 500 msec to 0 μV, respectively. For each epoch, power was calculated by the EEGLAB MatLab toolbox (Delorme & Makeig, 2004) using Morlet wavelets in 91 logarithmically spaced frequency bins between 2.4 and 150 Hz, with wavelet cycle numbers ranging from 3 to 12. Time intervals of 685 msec were dropped from both sides of the epoch. The remaining 3630 msec were divided into 600 time bins. All measures of power were expressed in decibels (dB) as a logarithm of the power amplitude multiplied by 10. Evoked power was calculated by averaging the raw data across trials, and taking the power of that averaged data. For induced activity, the power of individual trials was taken and averaged, and then the part attributable to evoked activity was subtracted. In order to compute the power spectral density, the mean of total power between −1100 and −100 msec was averaged. Event-related spectral perturbations (ERSP) were calculated by averaging power relative to the mean

baseline between −1100 and −100 msec. To confirm our results, we estimated the envelope of the amplitude of band-pass filtered signal using analytical amplitude as previously performed by Freeman (2004). Briefly, the raw signal was band-pass filtered using a two-way least-squares FIR filter in three frequency ranges: low theta (3–5 Hz), high theta (6–12 Hz), and gamma (30–80 Hz). Subsequently, the signal envelope was extracted by calculating the module of the Hilbert transform. Statistical analysis was performed using the permutation method (Westfall & Young, 1993) with 10,000 iterations. Nonpaired and paired *t* tests were used for the saline/ketamine factor, and the after-event/baseline factor, respectively. This method keeps the family-wise error type II at the desired level for multiple comparisons in the time or frequency domain. We do not report statistically significant changes shorter then 10 msec. For evoked power analysis, the ANOVA repeated measure of averaged squared analytical amplitude was calculated using JMP in time intervals 0–60 and 515–575 msec. The power of statistical test was stronger in the case of the power spectral density than analytical amplitude because the former contains data accumulated over relatively long time interval.

RESULTS

There was no effect of ketamine on locomotor activity at these subanesthetic doses [$F(2, 15) = 1.67$, $p = .22$; mean ± *SEM*: saline 2721 ± 333.7, 5 mg/kg ketamine 2270 ± 341.9, 20 mg/kg ketamine 3324 ± 524.5]. The qualitative pattern of ERPs is demonstrated in Figure 2. The authors have previously published the effects of ketamine on the amplitude and latency of time-locked averaged activity in the time domain (Maxwell, Ehrlichman, Liang, Trief, et al., 2006; Connolly et al., 2004; Siegel et al., 2003). The current work focuses on the time–frequency domain to extend previous findings. Examples of single-trial recordings are shown in Figure 3. A clear change of rhythm due to the auditory clicks is evident in the saline condition. In the ketamine condition, a change in rhythm is almost nonexistent. Figure 1B demonstrates the pattern of theta-modulated gamma activity present in these recordings, indicating a large contribution of hippocampal activity to the overall signal.

Background Power

To investigate the effect of ketamine on background activity unrelated to the stimulus, the average power was calculated before the first click in the time window −1100 to −100 msec (Figure 4).

The dosage of 5 mg/kg ketamine yields a statistically significant increase in power in frequency range 33–93 Hz ($p < .001$) including the gamma range (30–80 Hz).

At 20 mg/kg, the increase in power additionally includes the frequency range 26.5–143 Hz ($p < .001$) including the gamma range. We note a statistically significant decrease

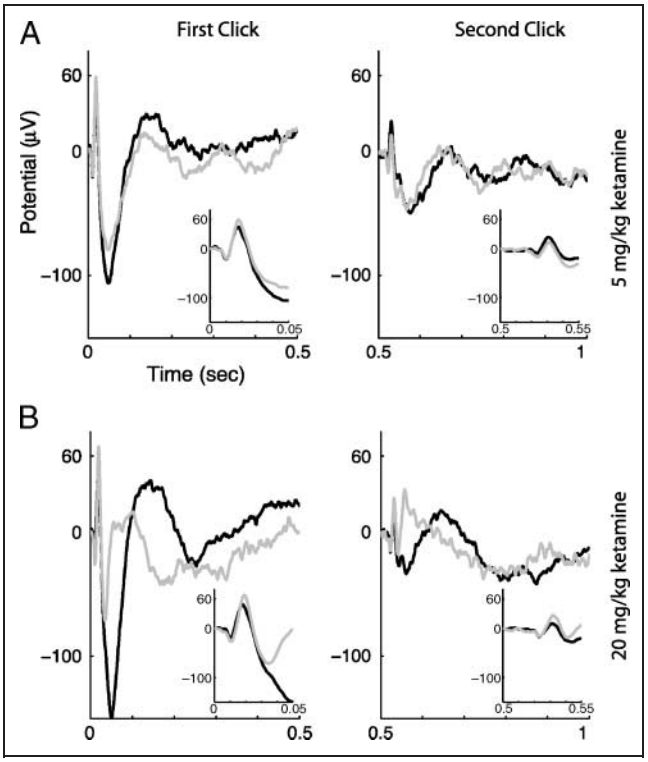

Figure 2. ERPs during the auditory paired-click task after saline (black lines) and ketamine (gray lines) injections with (A) 5 mg/kg and (B) 20 mg/kg. Left panel responses are shifted to 0 μV at the time of the first click (at 0 sec), and right panel responses are shifted to 0 μV at the time of the second click (at 0.5 sec). Inset shows zoom at 0–50 msec in each panel. ERPs were calculated averaged over 50 trials and across 8 animals.

in power within the frequency range 2.5–21 Hz ($p < .001$), which includes parts of the delta, theta, alpha, and beta frequency bands. The two curves cross near 23.5 Hz.

Evoked Power

ERSP (Figure 5) and analytic amplitude (Figure 6) for evoked power did not show a statistically significant effect between saline and 5 mg/kg ketamine ($p > .05$).

For 20 mg/kg ketamine, there was a decrease in low theta (3–5 Hz) [$F(1, 7) = 14.5, p < .01$] and high theta (6–12 Hz) power [$F(1, 7) = 6.2, p < .05$] in the time range 0–60 msec, and an increase in gamma power in time intervals 0–60 msec [$F(1, 7) = 12.7, p < .01$] and 515–575 msec [$F(1, 7) = 29.9$, $p < .001$].

Induced Power

Using induced ERSPs, two main effects ($p < .001$) are visible in the saline condition (Figure 7). There is an early burst of power near 20–40 msec in the 15–150 Hz frequency range, and a strong depression starting near 160 msec and lasting over 1 sec is pronounced in the 3–20 Hz frequency range. This depression has three visible peaks, the first two of which are near 300 msec at 4 Hz and 10 Hz

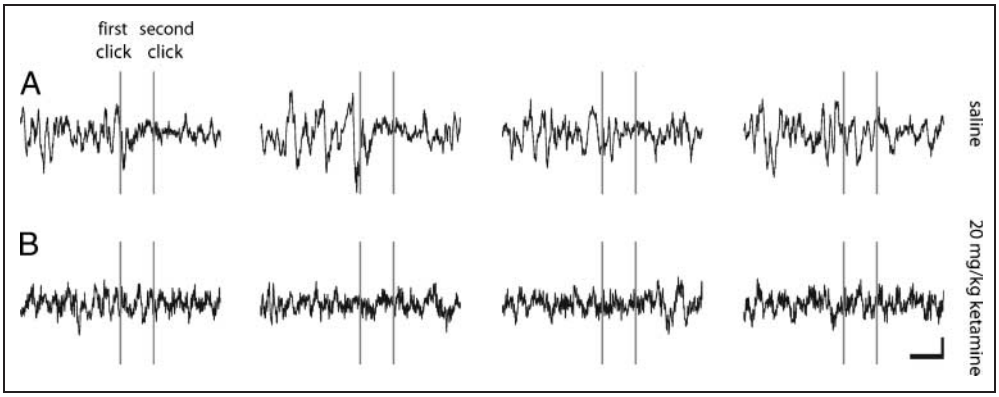

Figure 3. Example of five consecutive raw single-trial recordings (A) after saline and (B) ketamine injection. Horizontal scale line represents 500 msec and vertical line represents 250 μV. Two vertical lines represent the first and the second auditory clicks.

and the latter near 700–800 msec at 10 Hz. In the ketamine condition, the power burst in the early 20–40 msec interval is less pronounced, and in the 20-mg/kg ketamine condition, the late theta depression is lost.

To further quantify these changes, we calculated square analytic amplitude (Freeman, 2004) in three frequency bands: low theta (3–5 Hz), high theta (6–12 Hz), and gamma (30–80 Hz) (Figure 8). The family-wise error was set to a level of 0.01. At 5 mg/kg ketamine, excepting three short intervals in the gamma frequency range (135–155, 335–350, and 595–605 msec), there is no significant difference between the ketamine and saline conditions. In the saline condition for low theta, a significant attenuation of analytic amplitude from baseline is apparent in the time interval 155–400 msec. In the ketamine condition for low theta, the depression is slightly longer and localized in the time interval 125–730 msec. In the saline condition for high theta, the deviation from baseline is localized in the intervals 115–500, 600–920, and 990–1025 msec. In the ketamine condition for high theta, the power is depressed in the time interval 155–705 msec. The induced gamma frequency band shows an early increase from the baseline in the saline condition during 6–45 msec and in the ketamine condition during 10–36 msec.

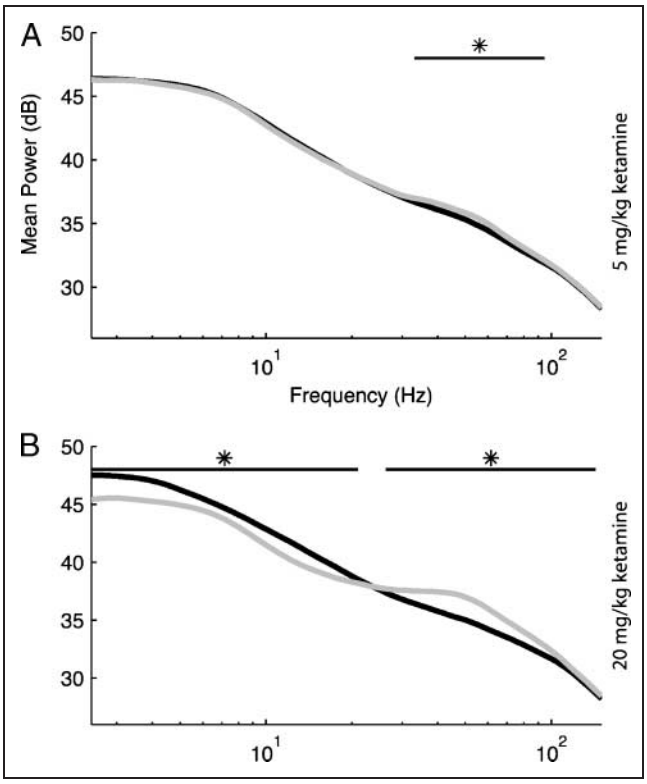

Figure 4. Power spectral densities calculated for intervals between −1100 and −100 msec before the first click (background data). Saline (black lines) and ketamine (gray lines) injection with (A) 5 mg/kg and (B) 20 mg/kg. Horizontal lines with star above represent frequency ranges with statistically significant differences between saline and ketamine conditions with $p < .001$. At (A) horizontal bar spreads from 33 to 95 Hz. At (B) the curve intersection is located about 23.5 Hz.

In contrast to 5 mg/kg, signal power at 20 mg/kg in the low theta saline and ketamine conditions are statistically different for all calculated time intervals. Low theta's depression from baseline in the saline condition is pronounced in the time interval 200–755 msec, but there is no statistically significant deviation from the baseline in the ketamine condition. For high theta, the two conditions are different except for two time intervals: 185–850 and 970–1360 msec. In the saline condition, power is depressed during the long time interval 115–1220 msec and, in the ketamine condition, power is depressed only briefly at 660–740 msec. For the gamma frequency range, the two conditions are statistically different except for the short time interval after the first click (14–52 msec) within which both the saline and ketamine conditions are attenuated during 10–47 and 13–29 msec, respectively. In the saline condition, for the gamma range during the time interval 100–1100 msec, power has intermittent depression from baseline that is not present in the ketamine condition, nor in the 5-mg/kg dataset.

Summary

Our results suggest the following findings.

- Ketamine produces a marked decrease in background theta (3–7 Hz, 8–12 Hz), and an increase in background gamma power (30–80 Hz).
- Evoked responses follow the background trend: 0–100 msec poststimulus theta evoked power is decreased, and gamma evoked power is increased.
- Induced responses in the gamma range have similar characteristics to background gamma power and evoked

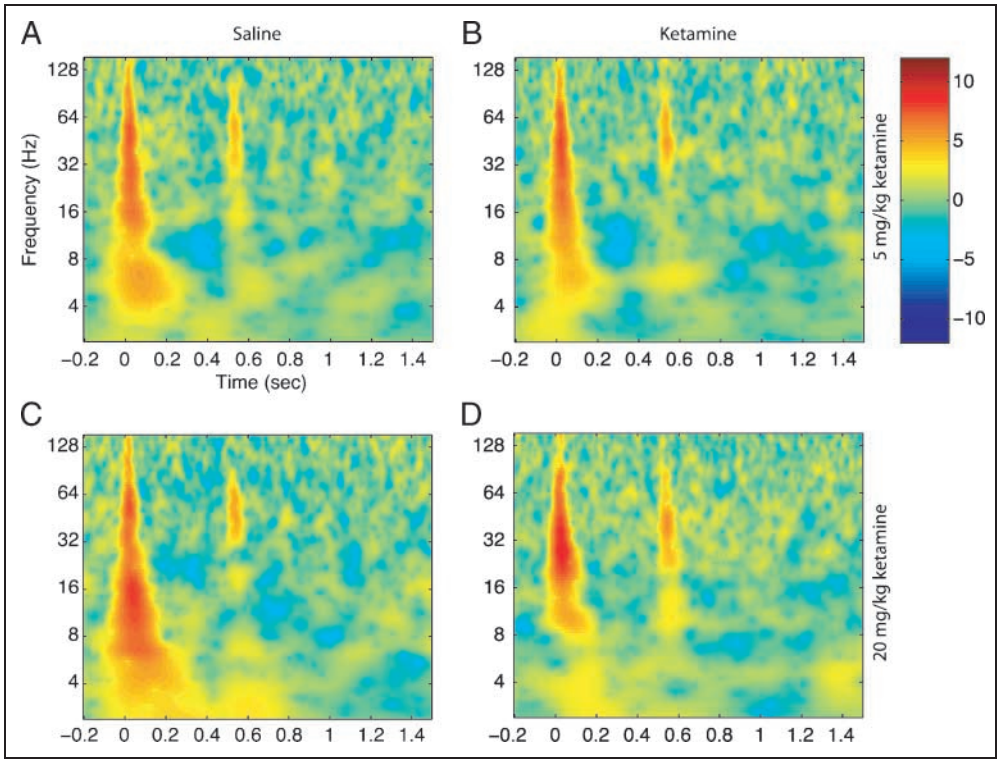

Figure 5. Evoked ERSPs. Colors represent average deviation in decibels (dB) from the mean baseline before the first click. (A) After saline (pre 5 mg ketamine), (B) after 5 mg/kg ketamine injection, (C) after saline (pre 20 mg ketamine), and (D) after 20 mg/kg ketamine injection.

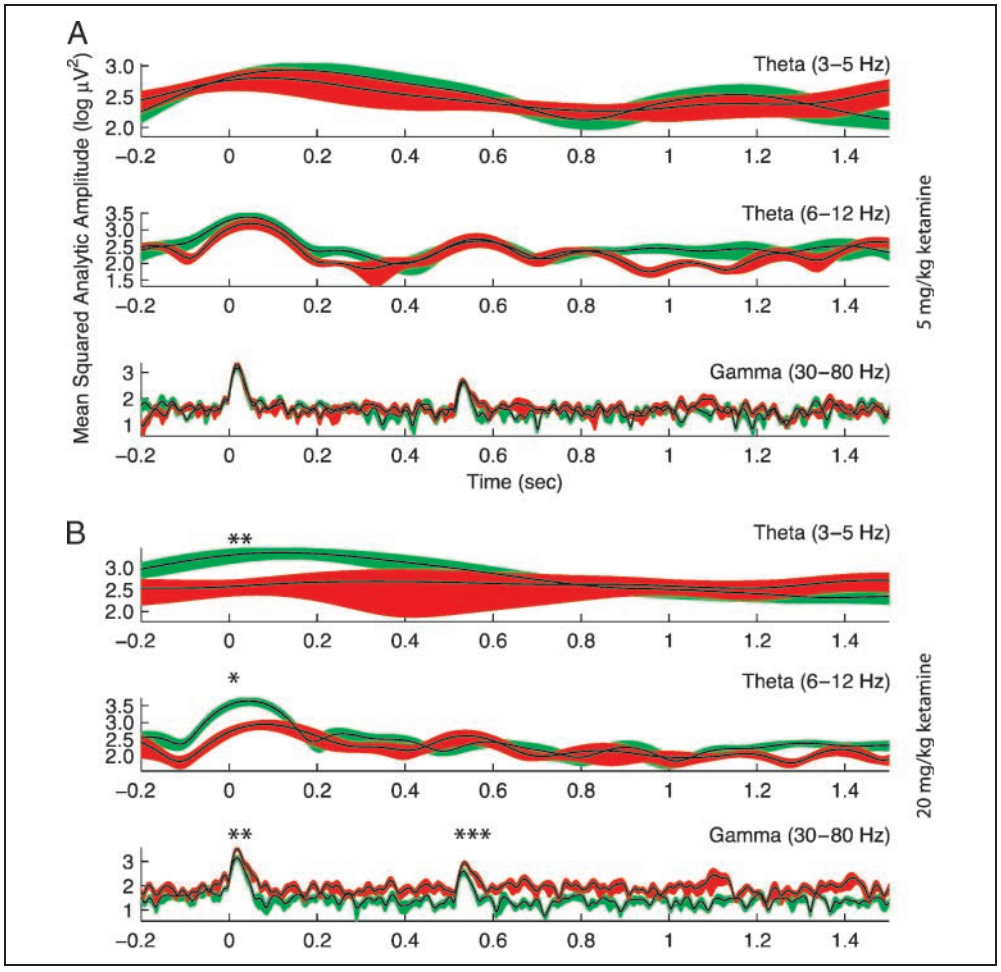

Figure 6. Evoked analytic amplitude calculated for three frequency bands: low theta (3–5 Hz), high theta (6–12 Hz), and gamma (30–80 Hz) after saline (green lines) and ketamine (red lines) injections with (A) 5 mg/kg and (B) 20 mg/kg. Width of the line indicates standard error of measurement (*SEM*). Stars mean statistically significant difference between saline and ketamine conditions (*$p < .05$, **$p < .01$, ***$p < .001$).

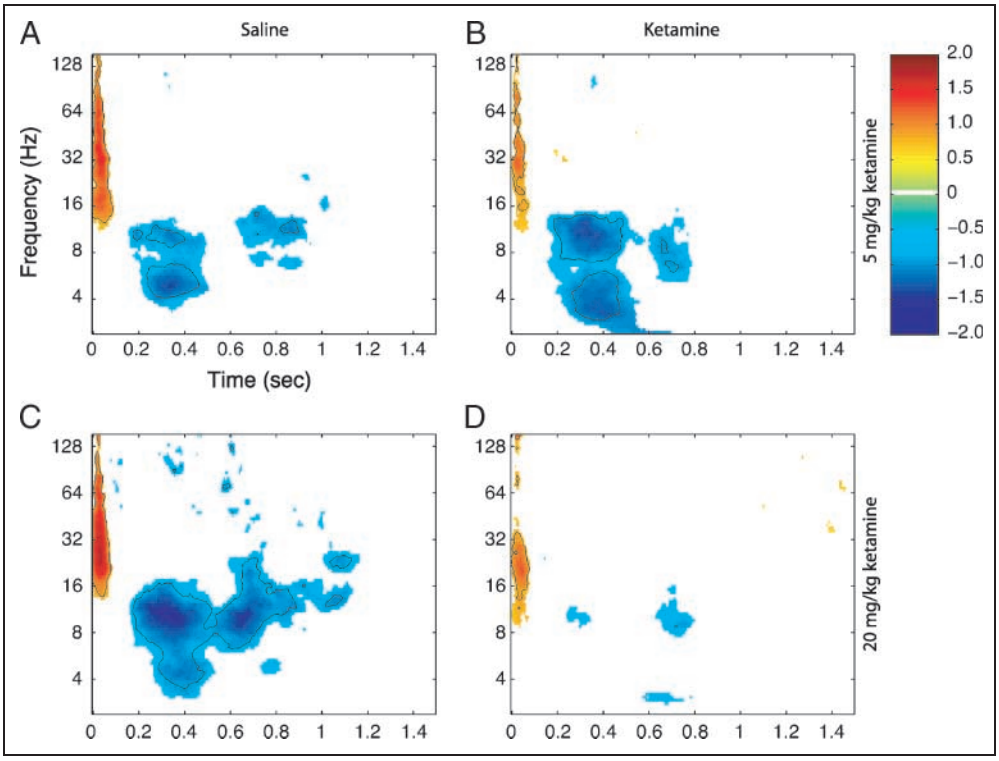

Figure 7. Induced ERSPs. Colors represent average deviation in decibels (dB) from the mean baseline before the first click. (A) After saline (pre 5 mg ketamine), (B) 5 mg/kg ketamine injection, (C) saline (pre 5 mg ketamine), (D) 20 mg/kg ketamine injection. Only statistically significant results are shown ($p < .05$). Black contour indicates statistical significance at the level of ($p < .001$).

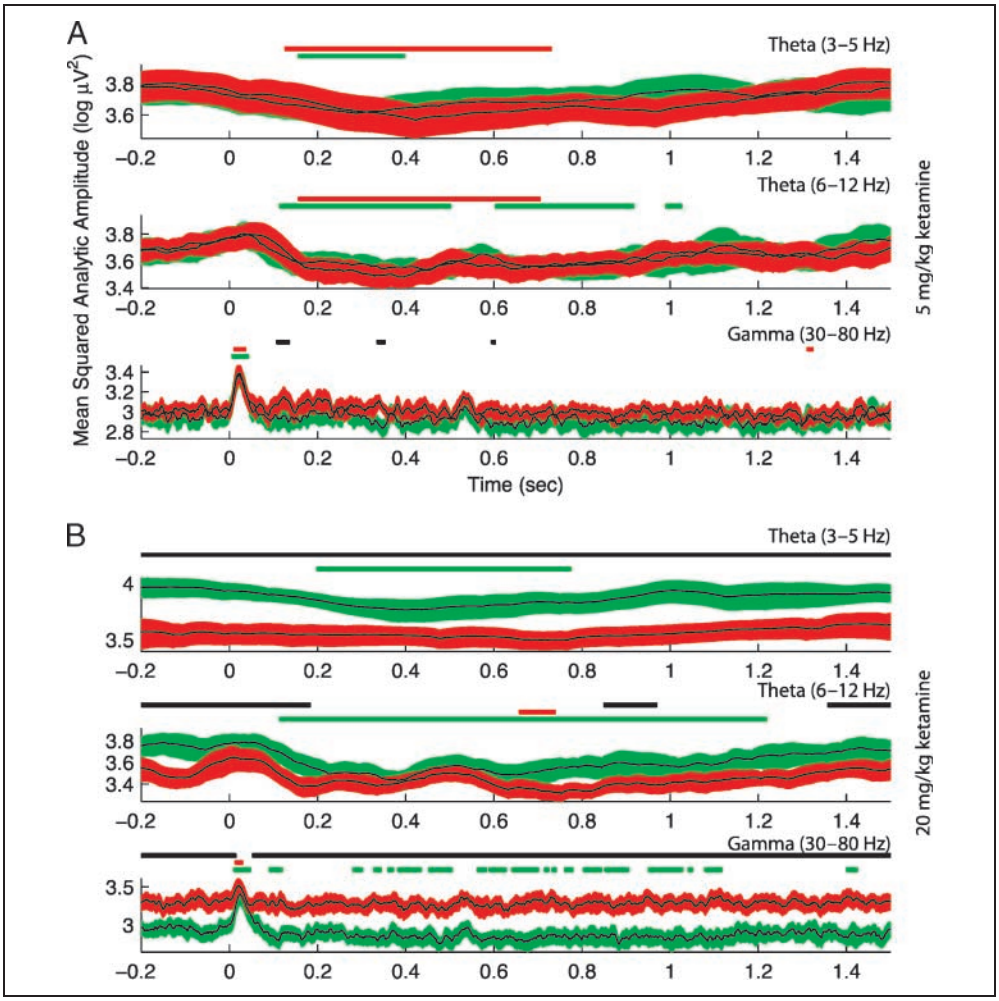

Figure 8. Induced analytic amplitude calculated for three frequency bands: low theta (3–5 Hz), high theta (6–12 Hz), and gamma (30–80 Hz) after saline (green lines) and ketamine (red lines) injections with (A) 5 mg/kg and (B) 20 mg/kg. Horizontal bars represent time ranges with statistically significant differences between saline and ketamine conditions (black line), saline condition and saline mean baseline (green line), and ketamine condition and ketamine mean baseline (red line) with $p < .01$. Width of the line indicates standard error of measurement (*SEM*).

responses. However changes relative to the background are reduced by ketamine.
- There is a clear suppression of induced theta power that persists for roughly 1000 msec in control animals, but this suppression is lost following ketamine.

DISCUSSION

Theta and Gamma Oscillations

We investigated the effect of ketamine during the auditory paired-click paradigm using two doses (5 and 20 mg/kg). We analyzed the relationship between background, evoked, and induced power before and after the auditory stimulus and their alteration in the presence of ketamine. We have specifically focused on the theta and gamma frequency ranges. Our results demonstrate that ketamine, in subanesthetic doses, produces complex changes in the network oscillatory activity of neurons, specifically in theta and gamma frequency ranges. These perturbations affected ongoing, background activity as well as event-related activities. Additionally, power values in the theta and gamma bands tended to move in opposite directions, which may be explained by the fact that oscillations in hippocampus in these frequency ranges may be interrelated (Chrobak & Buzsaki, 1998; Bragin et al., 1995; Llinas & Ribary, 1993; Soltesz & Deschenes, 1993; Woolley & Timiras, 1965). Of special note, ketamine attenuates the depression in late induced theta power, leaving only a short depressed activity after the second click located in the high theta frequency range. This may correlate with recent human EEG data showing a decrease in the 8–12 Hz total power during a P300 task in the control healthy group and an attenuation of this decrease in patients with schizophrenia (Ford, Roach, Hoffman, & Mathalon, 2008).

Because ketamine is thought to exert its effects via blocking NMDA receptors, these data support their role in mediating the balance between theta and gamma responses to sensory stimuli with implications for dysfunction in schizophrenia. We also observed that ketamine produced changes in the prestimulus power content, indicating that the state of the animal brain changed independent of the auditory stimuli used in the experiment. This makes the analysis of the event-related changes more complex, as changes in power relative to the background may depend upon their absolute values. We found an increase in power in the gamma frequency range (30–80 Hz) and a decrease in power in lower frequencies, including the theta range (low: 3–5 Hz; high: 6–12 Hz). The transition point between decrease and increase in power was located around 23.5 Hz. For the lower, subanesthetic concentration of 5 mg/kg ketamine, the only statistically significant change was the gamma power amplification. The increase of in vivo gamma power after ketamine administration in hippocampus was previously reported (Hinman et al., 2007; Ma & Leung, 2007). Magnetoencephalography studies suggested a positive correlation between theta power in the temporal lobe and positive symptoms such as hallucinations (Sperling, Bleich, Maihofner, & Reulbach, 2009; Ince, Goksu, Pellizzer, Tewfik, & Stephane, 2008; Fehr et al., 2001, 2003; Ishii et al., 2000; Sperling, Vieth, Martus, Demling, & Barocka, 1999; Canive et al., 1998). These studies suggest an opposite change in theta power than that reported here. It is not possible to evaluate the effects of ketamine on constructs such as hallucinations in our animals, complicating the ability to correlate our findings with symptomatic exacerbations in humans. Consistent with our results, Chrobak, Hinman, and Sabolek (2008) also demonstrated ketamine-induced changes in theta and gamma power, including a decoupling of the theta/gamma phase relationship in hippocampus.

Ketamine Mode of Action on Local Circuits

The nature of our electrode configuration allows for recording of activity throughout the entire brain. However, hippocampus is the main generator of theta rhythms (Buzsaki, 2002) and some investigators have argued that hippocampus contributes strongly to gating (Adler, Hoffer, Wiser, & Freedman, 1993). It has also been reported that the power of gamma oscillations is significantly higher in hippocampus than in the rest of the brain (Bartos, Vida, & Jonas, 2007). We propose that hippocampus contributes heavily to the activity in our recordings. Therefore, understanding the effect of ketamine on local hippocampal circuits may help interpret the observed changes in gamma and theta oscillatory power. We speculate that dysfunction of the glutamatergic system in schizophrenia affects theta/gamma oscillations on the level of this local circuit. In particular, we speculate that a disruption in the interaction between different subtypes of interneurons and pyramidal cells may mediate our observed oscillatory findings. This circuit has been shown to be disrupted in schizophrenia (Lewis, Hashimoto, & Volk, 2005) and it has also been shown to be a key generator of oscillatory activity in neuronal populations in vivo (Bartos et al., 2007). Ketamine likely targets NMDA receptors located at hippocampal interneurons (Greene, 2001), with an emphasis on O-LM cells (Tort, Rotstein, Dugladze, Gloveli, & Kopell, 2007) that contain an abundance of NMDA receptors (Nyiri et al., 2003; Hajos et al., 2002). These interneurons are 10-fold more sensitive to NMDA-receptor antagonists than pyramidal cells at low doses (Grunze et al., 1996).

We report significant changes in background gamma (increased) and background theta (decreased) activity with ketamine administration. In interpreting these results, it is interesting to note that at the level of hippocampus modulation of gamma and theta oscillations has been shown to be coupled. Data from in vitro preparations indicate that theta oscillations may be masked or inhibited by the presence of gamma oscillations (Gillies et al., 2002). An implication of this finding is that disruption of the hippocampal theta generator would have a secondary effect of unmasking background gamma activity (Gillies et al., 2002), increasing power in this frequency band. Although the precise mechanism of theta generation is unknown, hippocampal

O-LM cells are thought to be integrally involved (Traub, Bibbig, LeBeau, Buhl, & Whittington, 2004). O-LM cells are also known to contain an abundance of NMDA receptors (Tort et al., 2007), and thus, would likely be affected by ketamine or states of altered glutamatergic neurotransmission. The failure of the theta generator as a mechanism for the observed changes associated with ketamine is in agreement with the hypothesis that event-related theta oscillations have a double function in information processing: "filtering in" the first click, and "filtering out" the second click (Vinogradova, 1995). Although this is a plausible mechanistic explanation of our findings, further experimental work and computational modeling will be required to solidify these connections.

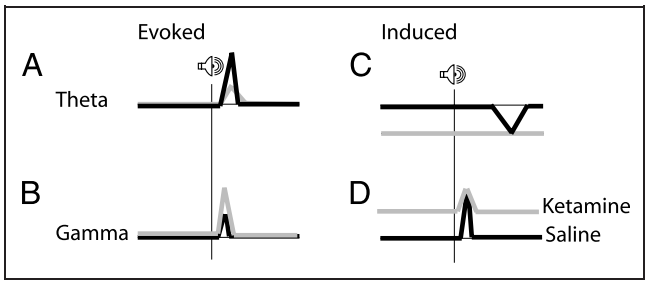

Figure 9. Summary of the absolute and relative changes in power before and after an event in the saline (green) and ketamine (red) conditions. (A) Theta evoked power, (B) gamma evoked power, (C) theta induced power, (D) gamma induced power.

Absolute vs. Relative Power

There is some variability in the literature regarding abnormalities in firing patterns observed in schizophrenia and in animal models of the disorder. In human EEG studies, there are reports of a gamma power decrease in schizophrenia patients (Ferrarelli et al., 2008; Gallinat, Winterer, Herrmann, & Senkowski, 2004), simultaneous decreases in the left hemisphere and frontal sites and an increase in right hemisphere and parieto-occipital sites (Haig et al., 2000), a decrease in gamma power associated with negative symptoms, and an increase in gamma power associated with positive symptoms (Herrmann & Demiralp, 2005; Lee et al., 2003).

Taking into account that, in an animal model of the disorder after acute injection of ketamine, a complex spectrum of changes is observed, we explored possible causes for the complexities regarding increases and decreases in signal power in the theta and gamma frequency ranges. Several measured or calculated values can be confused if not fully qualified: total power, evoked power, induced power, absolute power, and power relative to the background. First, using "relative to the background" versus "absolute change in power" may introduce divergent results, especially in tasks where the first factor is an external stimulus and the second factor is saline versus drug condition. In our data, the induced gamma power is a good example of this situation (Figure 8B). Short increases in the induced gamma power just after the first click reach statistically the same absolute value in the saline and ketamine condition, but the relative changes are different because they start from different prestimulus baselines. The total power in that case behaves identically (data not shown).

Additionally, four combinations of experimental conditions exist: before auditory stimulus when saline is injected, after auditory stimulus when saline is injected, before auditory stimulus when ketamine is injected, after auditory stimulus when ketamine is injected. In all of these four conditions, total/induced power of the field potential may differ. If A and B are two of these conditions and the background/induced power is larger in Condition B (Figure 9D, red color) than in Condition A (Figure 9D, green color), and relative-to-the-background change in power is larger in Condition A, it still may not be large enough to make the absolute power after the stimulus larger in the Condition A, than in the Condition B. Therefore, a comparison of relative changes of power needs to be evaluated in the context of changes of the background power. This complication does not apply to evoked power because the background evoked power comes close to zero.

In an animal model of schizophrenia, it is possible to perform a within-subjects experiment in which measurements of power are taken in all four conditions for each mouse. Human data in schizophrenia research come from a comparison of the control and patient groups before and after stimulus in a between-subjects experiment. It is not possible to make within-subject comparisons between control and schizophrenia conditions. Therefore, it is possible that, in the human experiments, the relative and absolute changes of power may be confounded, taking into account the large variability of spontaneous (background) power levels within a control and patient group. Data regarding the effects of schizophrenia on gamma oscillations are mixed. Some studies suggest reductions in gamma activity using a gamma frequency stimulus to evaluate entrainment. Others show reductions in evoked power, albeit after removal of baseline activity (Spencer et al., 2003, 2004; Kwon et al., 1999). Our group has found increased gamma power in schizophrenia, which is due to the increase in baseline (Turetsky & Siegel, 2007; Turetsky, McGue, Ramsey, Siegel, & Gur, 2006). Indeed, the variability in findings is largely a function of how each group handles background activity as its removal yields a reduction, but its inclusion yields the opposite finding.

Other Complexities

It may be that the local increase in gamma power (recorded by intracranial electrode) is associated with the global decrease in the gamma power (recorded by a scalp electrode) by breaking down the long-range synchronization in this frequency range (Yeragani, Cashmere, Miewald, Tancer, & Keshavan, 2006). It is conceivable that local changes in oscillations, such as an increase in gamma, may break down

the mechanisms for long-range synchronization, or inversely, the loss of long-range synchronization may cause a local, compensatory increase in gamma power. This may explain the decrease in gamma power in EEG recordings in patients with schizophrenia and the increase in power in potentials recorded in the animal models of schizophrenia. Another explanation may be that the effect of ketamine depends upon brain area and cortical layer (Roopun et al., 2008). An increase in gamma power after ketamine administration has also been found in neocortex (Pinault, 2008). In contrast, decreases in gamma power are seen in vitro in medial-temporal structures (Cunningham et al., 2006; Uhlhaas et al., 2006). Functional variability along the longitudinal axis of hippocampus has also been described (Kjelstrup et al., 2008); therefore, further investigation of ketamine action in these regions may confirm some of these possibilities.

Limitations

The use of a bipolar configuration spanning a negative pole adjacent to frontal cortex and a positive pole in hippocampus has both advantages and disadvantages. This configuration allows for a better translation to human EEG, which is subject to signals from multiple sources. However, our configuration does not allow for isolation of signals to a single, unitary source. As such, we are not suggesting that the observed EEG spectral analysis reflects only hippocampal activity. Rather, it reflects the gestalt of EEG signals that coalesce to yield the pattern of abnormalities in schizophrenia from these two perspectives. Of note, this configuration is most sensitive to the structures closest to the electrode tips, and therefore, does include activity from both hippocampus and frontal cortex. Because our goal is to examine the extent to which ketamine recapitulates the changes in gamma and theta oscillations in schizophrenia, this method is able to address the primary question posed in this study. Future studies could examine the regional source contributions of these abnormalities.

Summary

In summary, we found that after injection of ketamine, theta/gamma frequency oscillations display opposing effects that suggest possible fundamental alterations in information processing in schizophrenia.

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