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Ketamine supresses REM sleep and markedly increases EEG gamma oscillations in the Wistar Kyoto rat model of treatment-resistant depression

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ABSTRACT

Wistar–Kyoto (WKY) rats exhibit depression-like characteristics and decreased sensitivity to monoamine-based antidepressants, making them a suitable model of treatment-resistant depression (TRD). Ketamine has emerged recently as a rapidly acting antidepressant with high efficacy in TRD. Our aim was to determine whether subanaesthetic doses of ketamine can correct sleep and electroencephalogram (EEG) alterations in WKY rats and whether any ketamine-induced changes differentially affect WKY rats compared to Sprague-Dawley (SD) rats. Thus, we surgically implanted 8 SD and 8 WKY adult male rats with telemetry transmitters and recorded their EEG, electromyogram, and locomotor activity after vehicle or ketamine (3, 5 or 10 mg/kg, s.c.) treatment. We also monitored the plasma concentration of ketamine and its metabolites, norketamine and hydroxynorketamine in satellite animals. We found that WKY rats have an increased amount of rapid eye movement (REM) sleep, fragmented sleep-wake pattern, and increased EEG delta power during non-REM sleep compared to SD rats. Ketamine suppressed REM sleep and increased EEG gamma power during wakefulness in both strains, but the gamma increase was almost twice as large in WKY rats than in SD rats. Ketamine also increased beta oscillations, but only in WKY rats. These differences in sleep and EEG are unlikely to be caused by dissimilarities in ketamine metabolism as the plasma concentrations of ketamine and its metabolites were similar in both strains. Our data suggest an enhanced antidepressant-like response to ketamine in WKY rats, and further support the predictive validity of acute REM sleep suppression as a measure of antidepressant responsiveness.

1. Introduction

Major depressive disorder (MDD) is a complex mental disorder characterised by changes in mood and cognition that affects approximately 21 million people in the United States alone [1]. Disrupted sleep is one of the most common early features of depression that often precedes the core symptoms of the disease, and it is often an early sign of relapse preceding mood episode recurrences [2–4]. Still, sleep disturbances are often viewed as associated symptoms of the diseases, assuming that they would resolve with the treatment of core symptoms. The available clinical evidence suggests, however, that sleep disturbances contribute to the disease process and their treatment improves the outcomes of depression [5,6].

About 50% of people diagnosed with MDD receive conventional monoamine-based antidepressant treatment, but around 30% of them do not show improvement in their symptoms despite trying multiple, structurally distinct antidepressants [7]. These patients constitute the so-called 'Treatment Resistant Depression (TRD)' population. The N-methyl-D-aspartate (NMDA)-receptor antagonist ketamine has emerged recently as a rapidly acting antidepressant with high efficacy in TRD [8–10]. Although the precise mechanism of action of ketamine remains elusive [11], a growing body of clinical evidence suggests glutamatergic dysfunction in depression [12–14].

Endogenous animal models of TRD could provide a valuable tool for

Abbreviations: EEG, electroencephalogram; EMG, electromyogram; MDD, major depressive disorder; NMDA, N-methyl-D-aspartate; TRD, treatment-resistant depression; LMA, locomotor activity; WKY, Wistar-Kyoto; SD, Sprague-Dawley; PRF, pontine reticular formation; LDT, laterodorsal tegmental; PPT, pedunculopontine tegmental; REM, rapid eye movement; NREM, non-REM; GABA, gamma aminobutyric acid; s.c, subcutaneous.

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investigating novel therapeutics against TRD. One such promising model is the Wistar–Kyoto (WKY) rat, which shows depression-like neurochemical and behavioural characteristics as well as decreased sensitivity to monoamine-based antidepressants [15–19]. Compared to other strains such as Wistar, Fisher 344, Lewis and Sprague-Dawley (SD), the WKY rats display increased stress responses and anhedonia, learned helplessness, and increased depressive-like behaviours, and they are less responsive to monoamine-based antidepressants in the forced swim test of depression [16,18–23]. WKY rats also display depression-like sleep abnormalities that are less affected by serotonergic or noradrenergic antidepressants [24,25]. Alteration in glutamatergic signalling may also contribute to the depressive phenotype of WKY rats. Decreased NMDA receptor binding has been reported in WKY rats in brain regions also implicated in depression such as the prefrontal cortex, caudate putamen, nucleus accumbens and hippocampus [23,26,27].

The aim of the current study was to determine whether sub-anaesthetic doses of the glutamatergic NMDA receptor antagonist ketamine can correct the sleep and electroencephalogram (EEG) alterations seen in a rodent model of TRD (WKY) and whether the ketamine-induced changes in sleep and EEG differentially affect WKY rats in comparison to SD rats.

2. Methods

All experiments were conducted under the authority of United Kingdom Animals (Scientific Procedures) Act 1986 and with the approval of Royal Veterinary Colleges' Animal Welfare and Ethical Review Body and are in compliance with the ARRIVE guidelines. Adult male Sprague Dawley (SD; 200–250 g, Charles River, UK), and Wistar Kyoto (WKY; 200–250 g; Envigo, UK) rats were pair housed within their own strain with environmental enrichment and maintained on a standard 12 h light/dark cycle with food/water available ad libitum.

2.1. Surgery and EEG/EMG recordings

After a minimum of 2 weeks of acclimatisation to environmental conditions, we implanted 8 SD and 8 WKY rats with telemetry transmitters, and with EEG and electromyogram (EMG) electrodes under isoflurane anaesthesia (2–5%). Specifically, we placed a telemetry transmitter (HD-S02; Data Sciences International, St. Paul, MN, USA) into the peritoneal cavity and the tip of EEG leads epidurally over the frontal (2 mm anterior / 1 mm lateral to Bregma) and parietal (0 mm anterior / 1.5 mm lateral to Lambda) cortices of the left hemisphere for frontoparietal EEG recordings. EMG signals were acquired by a second pair of stainless-steel spring wires inserted into the neck extensor muscles.

After a recovery period of 7–10 days, the rats were placed individually in recording chambers in a sound-attenuated room with a 12:12 h light-dark cycle, constant temperature (21 ± 1 °C), with food and water available ad libitum, and EEG, EMG and locomotor activity (LMA) were recorded for 0.5 h before and 24 h after treatments. EEG, EMG and LMA were detected by an antenna (RPC-1, Data Sciences International, St. Paul, MN, USA) placed below the recording cages. EEG/EMG signals were amplified, analogue filtered (built-in frequency response: 0.5–100 Hz), digitized (500 Hz), and recorded alongside LMA on a computer for offline analysis (Spike2; CED, Cambridge, UK).

2.2. Drug treatment

We treated both SD and WKY rats with 3 different doses of ketamine [3, 5 and 10 mg/kg, subcutaneously (s.c.); Sigma-Aldrich, Gillingham, UK] or vehicle (0.9% saline; 2 ml/kg, s.c.) 3 h after light onset [Zeitgeber time 03:00 (ZT03)]. The different doses of ketamine and its vehicle were given to SD and WKY rats in a crossover design and in a randomized order, with 6–8 days between treatments. The doses were chosen based on the literature [28,29] and our pilot experiments (data not shown).

In addition, we treated a satellite group of SD and WKY rats (n = 9 each) with ketamine (3, 5 and 10 mg/kg, s.c.) and collected blood samples by venepuncture at 0.5, 1, 2 and 3 h post-treatment for pharmacokinetics profiling of ketamine an its major metabolites. 4 h after ketamine treatment, the rats were euthanized by CO_2 exsanguination and terminal blood samples were collected by cardiac puncture into K_2EDTA tubes for plasma isolation.

2.3. Quantification of ketamine and its metabolites by LC-MS/MS

Ketamine is metabolised to norketamine (NK), and norketamine is further metabolised to the hydroxynorketamine (HNK), and both metabolites are pharmacologically active [30]. Thus, alongside ketamine we also measured the concentration of its metabolites, NK and HNK, in the plasma samples. We analysed the plasma samples on an AB Sciex API4000 QTRAP liquid chromatography/mass spectrometry (LC-MS/MS) system equipped with an ESI source in positive ion mode and coupled to an Agilent 1200 liquid chromatographic system. The chromatographic separation was performed on an Aquasil C18 column (2.1 × 50 mm, 5 μm) at 25 °C using gradient elution with a 0.8 ml/min flow rate. The mobile phases A and B were 10 mM ammonium acetate in water and acetonitrile, respectively. The multiple reaction monitoring (MRM) parameters for ketamine and its metabolites, NK and HNK, with their respective internal standards (IS, shown in brackets) were: ketamine m/z 238.1 →125.1 (ketamine-d_4 IS m/z 242.1 →129.1), NK m/z 224.1→125.1 (NK-d_4 IS m/z 228.1 →129.0) and HNK m/z 240.1→125.0 (fenoterol IS m/z 304.1 →107.1). The calibration dynamic range was 0.2–5000 ng/ml for ketamine and 0.5–5000 ng/ml for NK and HNK.

2.4. Data analysis and statistics

EEG and EMG signals were resampled at 256 Hz, digitally filtered (EEG: 0.5–100 Hz; EMG: 5–100 Hz), and semi-automatically scored as wake, rapid eye movement (REM) sleep or non-REM (NREM) sleep, in 10-s epochs using SleepSign (Kissei Comtec, Matsumoto, Japan). An experienced scorer, blinded to treatment condition, visually inspected these preliminary scorings and made corrections when appropriate. We then measured the duration and number of bouts, and calculated the time spent in each behavioural state after treatment. To measure the propensity for NREM and REM sleep, we also calculated the latency to NREM and REM sleep onset for each rat. This was measured from the time of drug administration to the first six continuous 10 s epochs scored as NREM sleep or to the first three continuous 10 s epochs scored as REM sleep, respectively.

To reveal the changes in the frequency content of the recorded signal, we also performed a power spectral analysis of the EEG. EEG power spectra were computed for artifact-free 2-s epochs in the 0.5–100 Hz frequency range by fast Fourier transformation with a frequency resolution of 0.5 Hz. Before fast Fourier transformation, a window weighting function (Hanning) was applied. Epochs with movement-induced and other artefacts were discarded on the basis of the polygraph records. The values of consecutive 2-s EEG epochs per vigilance states were averaged over 2 h after the treatments. To reveal the changes in specific frequency bands after the treatments, we compared the discrete changes in the delta (0.5–4 Hz), theta (4–10 Hz), sigma (10–15 Hz), beta (15–30 Hz) and gamma band (30–100 Hz) of the EEG during wakefulness and NREM sleep. Due to the limited number of REM sleep episodes available, no power spectral analysis was performed on REM sleep EEG during the 2 h post-treatment period. In addition to vigilance state specific analysis, we also calculated the spectral values in the gamma frequency band regardless of vigilance states 0.5 h before and 5 h after treatments. For graphical presentation, we normalized the gamma power values of ketamine (3, 5 and 10 mg/kg, s.c.) treatment to the values of vehicle treatment in the same animal (100%).

To compare statistically the vigilance state parameters and raw EEG power spectral values, we used multivariate analysis of variance with

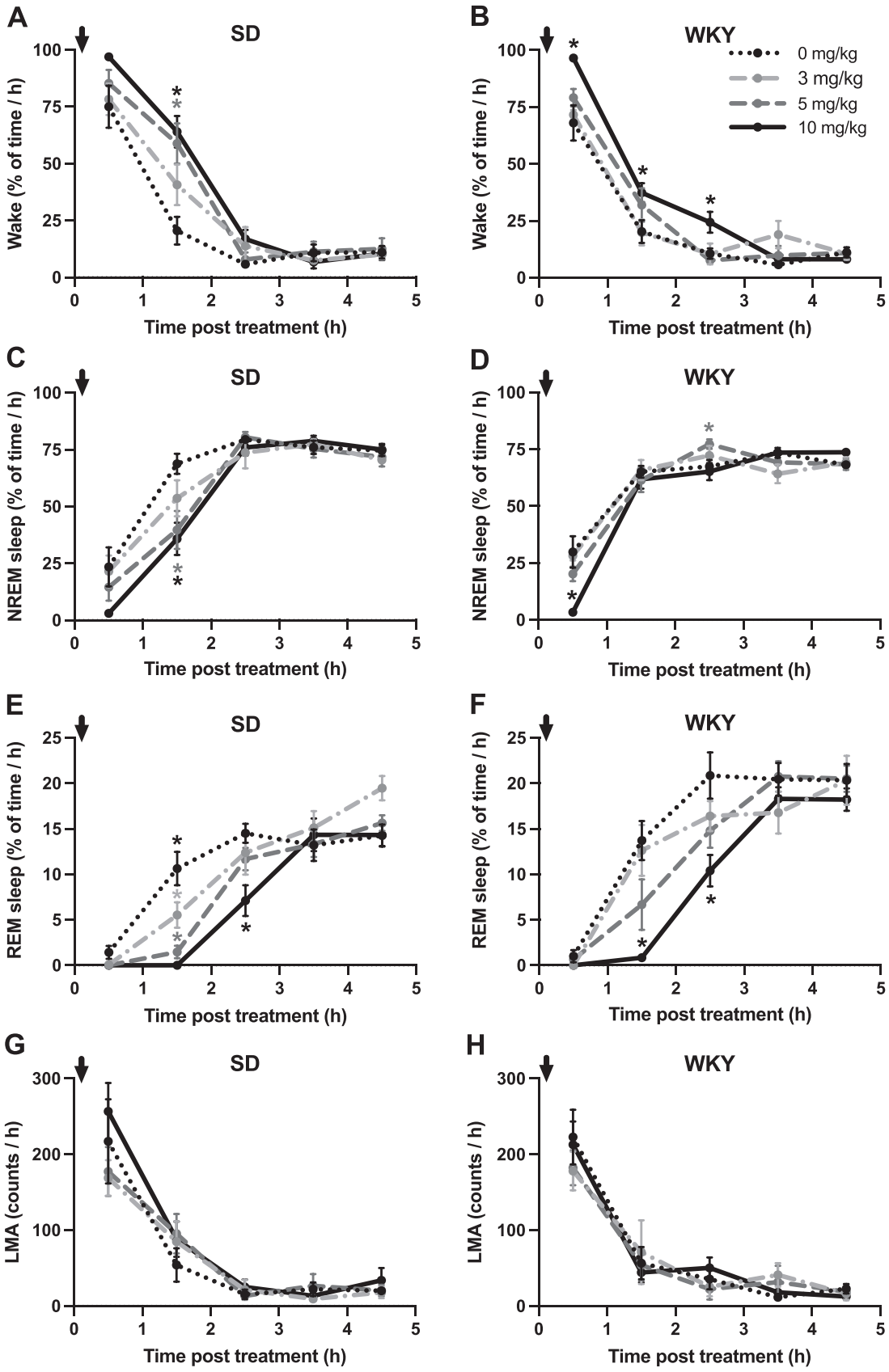

Fig. 1. Ketamine increased the amount of wakefulness and reduced REM sleep, but it had no effect on locomotor activity (LMA) in SD and WKY rats. The hourly amounts of wake (A, B), NREM sleep (C, D), REM sleep (E, F) and LMA (G, H) are shown in SD (A, C, E, G) and WKY (B, D, F, H) rats after treatment (arrow) with ketamine (3, 5 and 10 mg/kg; s.c.) or its vehicle (0 mg/kg, s.c.). Data are presented as mean ± SEM. *P < 0.05 vs vehicle treatment (Dunnett post-test).

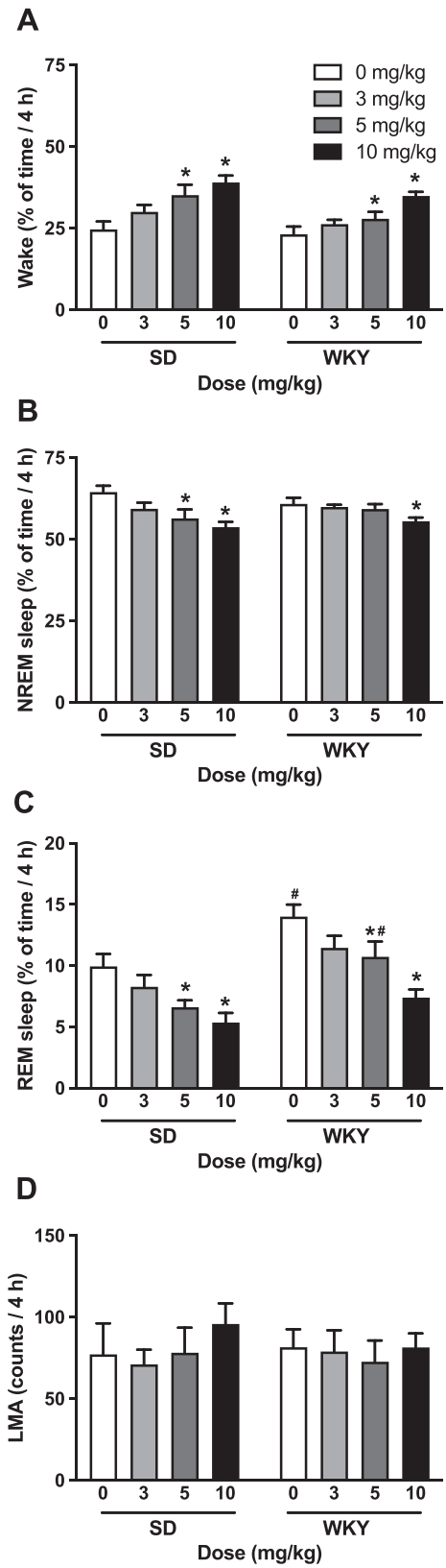

Fig. 2. Ketamine suppressed the abnormally increased amount of REM sleep in WKY rats in a dose-dependent manner. Changes in the percentage of wakefulness (A), NREM sleep (B), REM sleep (C) and LMA (D) are shown in SD and WKY rats during the first 4 h after treatment with vehicle (0 mg/kg, s.c.) or ketamine (3, 5 and 10 mg/kg; s.c.). Data are presented as mean ± SEM. *P < 0.05 vs vehicle treatment (Dunnett post-test); #P < 0.05 SD vs WKY of the same treatment (Sidak post-test).

repeated measures or mixed effects model where values were missing, which was followed by Dunnett or Šidak tests for post hoc comparisons (Prism 9.4; GraphPad, San Diego, CA USA). The results were considered statistically significant at $p < 0.05$. All results were expressed as means ± SEM.

3. Results

3.1. Ketamine suppresses REM sleep in WKY rats

At subanaesthetic doses, ketamine increased the time spent awake at the expense of NREM and REM sleep in both SD and WKY rats mainly within the first 4 h after the treatment [drug effects: $F_{(2.21,15.48)} = 8.69$, $p < 0.01$ (Fig. 1A); $F_{(2.15,15.06)} = 11.11$, $p < 0.01$ (Fig. 1B); $F_{(2.25,15.75)} = 5.99$, $p < 0.01$ (Fig. 1C); $F_{(2.35,16.48)} = 6.17$, $p < 0.01$ (Fig. 1D); $F_{(2.22,15.51)} = 9.13$, $p < 0.01$ (Fig. 1E); $F_{(1.76,12.31)} = 7.68$, $p < 0.01$ (Fig. 1F)]. Although the amounts of wakefulness and NREM sleep were similar in SD and WKY rats after vehicle treatment (Fig. 2A and B), WKY rats had 41% more REM sleep than SD rats early in the light period (ZT03–07), which is the passive phase in the rats [strain effect: $F_{(1,14)} = 13.38$, $p < 0.01$ (Fig. 2C)]. In addition, WKY rats had a fragmented sleep-wake pattern that was shown by the shorter and increased number of NREM sleep bouts (−35% and +47%, respectively) and by the increased number of wake bouts (+67%) compared to SD rats [strain effect: $F_{(1,14)} = 39.42$, $p < 0.01$; $F_{(1,14)} = 89.14$, $p < 0.01$; and $F_{(1,14)} = 85.60$, $p < 0.01$, respectively (Table 1)].

Acute treatment with subanaesthetic doses of ketamine decreased the amount of REM sleep in both SD and WKY rats in a dose-dependent manner [drug effect: $F_{(3,42)} = 18.89$, $p < 0.01$ (Fig. 2C)]. Ketamine reduced the amount of REM sleep by supressing its initiation, as shown by the dose-dependent increase in the latency to REM sleep onset, and by the decrease in REM sleep bout numbers in both SD and WKY rats [drug effects: $F_{(3,42)} = 34.23$, $p < 0.01$ (Fig. 3B) and $F_{(3,42)} = 23.21$, $p < 0.01$ (Table 1), respectively]. Besides supressing REM sleep, ketamine also increased the time spent awake and reduced the amount of NREM sleep in a dose-dependent manner during the first 4 h after the treatment in both SD and WKY rats [drug effects: $F_{(3,45)} = 18.33$, $p < 0.01$ and $F_{(3,42)} = 10.18$, $p < 0.01$, respectively (Fig. 2A and B)]. Ketamine supressed the initiation of NREM sleep, as shown by the dose-dependent decrease in the number of NREM sleep bouts in both SD and WKY rats [drug effect: $F_{(3,42)} = 20.44$, $p < 0.01$ (Table 1)]. In WKY rats, ketamine also increased the latency to NREM sleep onset [drug effects: $F_{(3,42)} = 5.89$, $p < 0.01$ (Fig. 3A)]. Interestingly in SD rats, ketamine (10 mg/kg, s.c.) not only decreased the number of wake, NREM and REM sleep bouts, but it also increased their mean duration, which resulted in a more consolidated sleep-wake pattern [drug effects: $F_{(3,42)} = 11.35$, $p < 0.01$; $F_{(3,42)} = 8.80$, $p < 0.01$ and $F_{(3,42)} = 3.87$, $p < 0.05$, respectively (Table 1)]. In contrast, the fragmented sleep-wake behaviour seen in WKY rats improved only partially after ketamine treatment as ketamine decreased the number of NREM and REM sleep bouts, but it had no effect on their durations [drug effects: $F_{(3,42)} = 20.44$, $p < 0.01$ and $F_{(3,42)} = 23.21$, $p < 0.01$, respectively (Table 1)].

Although ketamine may induce robust behavioural changes in rodents especially at higher doses [31], it did not alter LMA in either SD or WKY rats in this study at the doses tested (Figs. 1G and H, and 2D).

3.2. Eminent increase in EEG gamma oscillations in WKY rats after ketamine treatment

Since ketamine virtually abolished REM sleep in both SD and WKY rats for about two hours post- treatment in our study (Fig. 1E and F), we analysed the changes in EEG power spectra only during wakefulness and NREM sleep. Apart from the increased delta oscillations in WKY rats during NREM sleep [strain effect: $F_{(1,14)} = 13.12$, $p < 0.01$ (Fig. 4B)], there were no other differences in EEG power spectra between the two strains. Ketamine, however, differentially affected the EEG oscillations

Table 1
Vigilance state parameters in SD and WKY rats after vehicle or ketamine treatment.

Strain	SD				WKY			
Dose	Vehicle	3 mg/kg	5 mg/kg	10 mg/kg	Vehicle	3 mg/kg	5 mg/kg	10 mg/kg
Mean bout duration (min)								
WAKE	13.4 ± 2.8	14.9 ± 1.1	21.9 ± 2.4	39.4 ± 8.0[a]	6.7 ± 0.6	7.7 ± 0.7	9.3 ± 0.9[b]	13.8 ± 1.3[b]
NREM sleep	20.2 ± 1.3	19.3 ± 1.2	23.7 ± 2.3	29.5 ± 2.8[a]	13.1 ± 1.0[b]	12.5 ± 0.8[b]	15.0 ± 1.1[b]	14.9 ± 0.9[b]
REM sleep	7.6 ± 0.3	7.9 ± 0.6	8.6 ± 0.7	10.4 ± 1.0[a]	9.7 ± 0.7	9.5 ± 0.4	10.9 ± 0.3	9.7 ± 0.8
Number of bouts								
WAKE	33.1 ± 2.6	34.6 ± 2.4	27.1 ± 1.4	20.6 ± 3.0[a]	55.4 ± 3.6[b]	59.4 ± 5.7[b]	50.3 ± 3.3[b]	44.9 ± 2.6[b]
NREM sleep	45.3 ± 2.9	43.3 ± 2.6	32.8 ± 1.7[a]	25.4 ± 2.8[a]	66.4 ± 3.2[b]	68.4 ± 3.8[b]	56.3 ± 3.6[a,b]	50.3 ± 2.8[a,b]
REM sleep	19.0 ± 1.8	15.0 ± 1.3	11.3 ± 0.6[a]	7.5 ± 0.8[a]	21.1 ± 1.6	17.8 ± 1.8	14.1 ± 1.5[a]	11.4 ± 1.4[a]

Mean duration and number of bouts in each state during the first 4 h after vehicle or ketamine treatment. Results are shown as mean ± SEM. [a]$P < 0.05$ compared to vehicle (Veh) treatment of the same strain. [b]$P < 0.05$ SD vs WKY of the same treatment (Dunnett post-test).

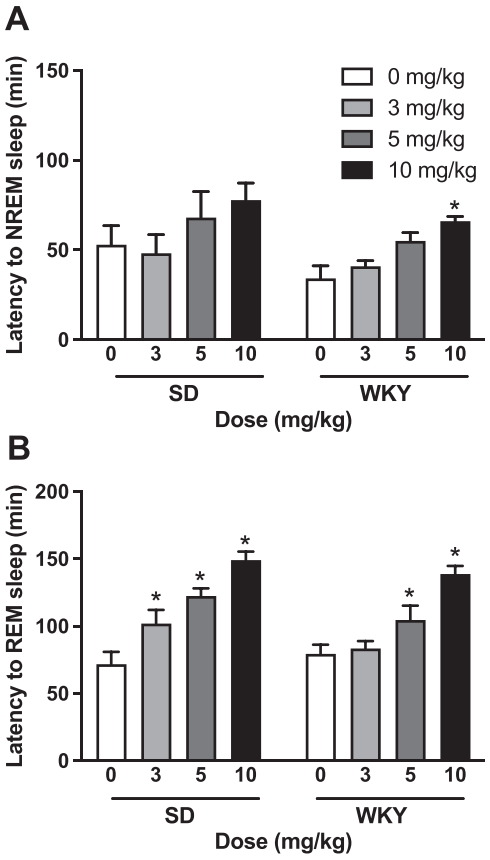

Fig. 3. Treatment with ketamine produced a dose-dependent increase in REM sleep latency in both SD and WKY rats. Changes in latencies to NREM (A) and REM (B) sleep onset are shown in SD and WKY rats after treatment with vehicle (0 mg/kg, s.c.) or ketamine (3, 5 and 10 mg/kg; s.c.). Data are presented as mean ± SEM. *P < 0.05 vs vehicle treatment (Dunnett post-test).

in SD and WKY rats (Figs. 4 and 5). While ketamine had no effect on EEG theta power in any of the strains during wakefulness (Fig. 4 A), it approximately doubled the wake-EEG gamma power in SD rats (+110%), and it more than tripled it in WKY rats (+244%) within the first two hours post-treatment [drug x strain interaction: $F_{(3,42)} = 7.53$, $p < 0.01$ (Fig. 4E)]. In addition, ketamine also increased beta power in the wake-EEG of WKY rats, but not of SD rats [drug effect: $F_{(3,42)} = 5.822$, $p < 0.01$ (Fig. 4 C)]. Ketamine's effect on EEG power spectra was not only strain, but also vigilance state specific. During NREM sleep, ketamine increased gamma and supressed sigma power in SD rats, but it had no effect on EEG oscillations in WKY rats, leaving the abnormally increased delta power largely unaffected in WKY rats [drug effects: $F_{(3,42)} = 3.34$, $p < 0.05$ and $F_{(3,42)} = 9.93$, $p < 0.01$, respectively (Fig. 4B, D and F)].

To examine whether the strain specific differences in the ketamine-induced gamma power increase are due to a delayed response in SD rats compared to WKY rats, we also analysed the time course of changes in this frequency band before and after the treatment and irrespective of vigilance states. We found that the maximum increase in EEG gamma power occurred within the 1st h, and extended into the 2nd h post-treatment in both SD and WKY rats, suggesting a similar pharmacokinetics profile of ketamine in the both WKY and SD strains [drug x time interactions: $F_{(1.34,9.37)} = 12.69$, $p < 0.01$ and $F_{(1.151,8.055)} = 29.53$, $p < 0.01$, respectively (Fig. 5A and B)].

3.3. The plasma concentrations of ketamine and its metabolites were generally similar in both SD and WKY rats after treatment

To determine whether there are strain-specific differences in ketamine metabolism, we also measured the plasma concentrations of ketamine and its major metabolites, NK and HNK, during the first 4 h post-treatment (Fig. 6). The plasma concentrations of ketamine were similar between SD and WKY rats after all three (3, 5 and 10 mg/kg, s.c.) doses of the drug and at any measured time points (Fig. 6A-B). Compared to SD rats, the plasma level of NK increased transiently in WKY rats 0.5 h after treatment with 5 mg/kg (s.c.) ketamine [time x strain interaction: $F_{(4,14)} = 19.58$, $p < 0.01$ (Fig. 6E)]. WKY rats also had a higher plasma level of HNK than SD rats 4 h after treatment with the highest (10 mg/kg, s.c.) dose of ketamine [strain effect: $F_{(1,\ 4)} = 8.69$, $p < 0.05$ (Fig. 6I)]. The plasma levels of both NK and HNK were similar in both strains at any other measured time points.

4. Discussion

We found that the amount of REM sleep is increased in WKY rats compared to SD rats. WKY rats also have a fragmented sleep-wake pattern and increased delta oscillations during NREM sleep. Sub-anaesthetic doses of the glutamatergic NMDA receptor antagonist ketamine decreased the amount of REM sleep in both WKY and SD rats, primarily by supressing its initiation. This was shown by an increase in the latency to REM sleep onset, and a decrease in the number of REM sleep bouts after ketamine treatment. Ketamine also increased the time spent awake and EEG gamma power during wakefulness in both SD and WKY rats, but it had no effect on LMA. More importantly, the ketamine-induced increase in EEG gamma power was almost twice as high in WKY rats as in SD rats despite of the generally similar plasma levels of ketamine and its metabolites, NK and NHK, in both strains.

Alterations in REM sleep, including shortened REM sleep latency and increased REM sleep amount, are among the most consistent findings in depression [32,33]. Total sleep deprivation as well as selective REM sleep deprivation rapidly alleviate the symptoms of depression [34,35]. Furthermore, most antidepressants that are structurally and pharmacologically different, suppress REM sleep in both healthy volunteers and depressed patients early in the treatment, which effect gradually

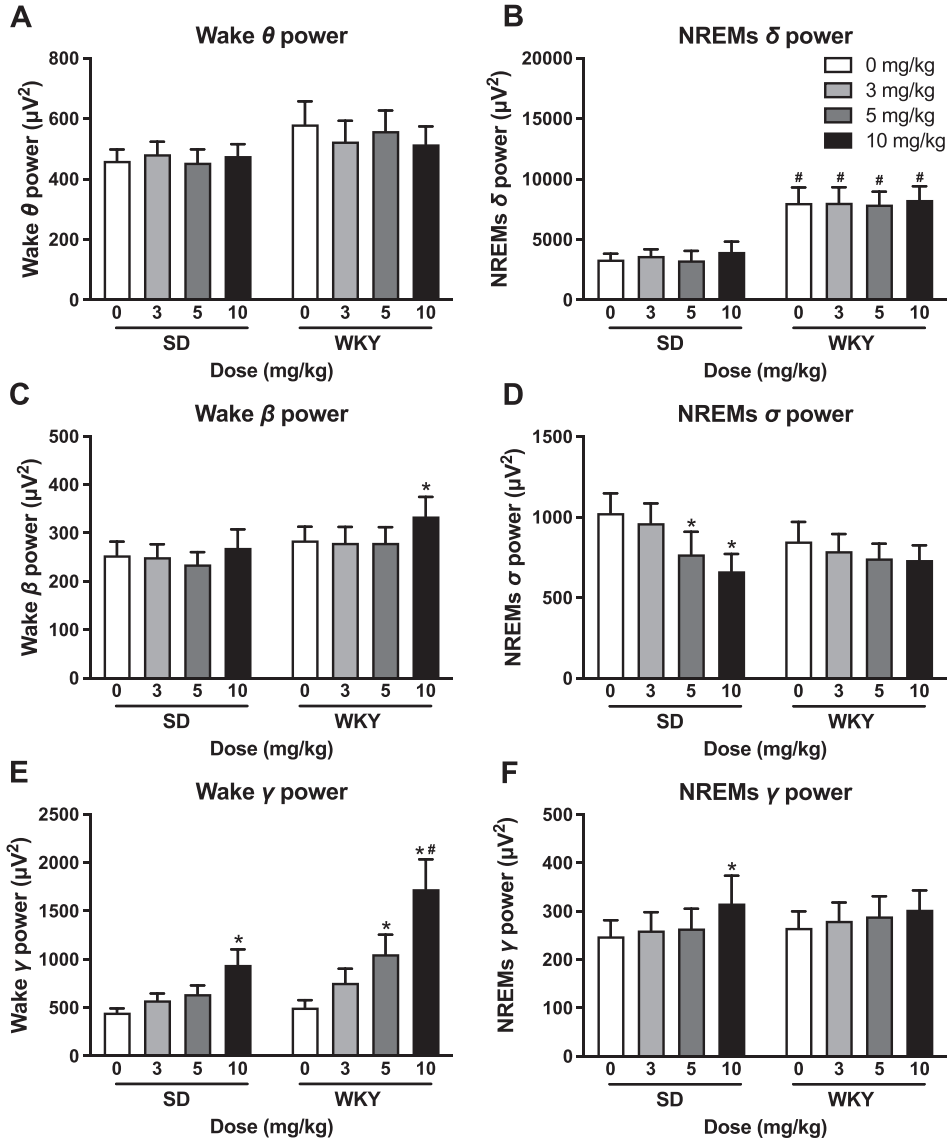

Fig. 4. Ketamine increased high frequency (beta and gamma) EEG oscillations in WKY rats during wakefulness. Changes in wake-EEG theta (A), beta (C) and gamma power (E) as well as in NREM sleep-EEG delta (B), sigma (D) and gamma power (F) are shown in SD and WKY rats during the first 2 h after treatment with vehicle (0 mg/kg, s.c.) or ketamine (3, 5 and 10 mg/kg; s.c.). Data are presented as mean ± SEM. *P < 0.05 vs vehicle treatment (Dunnett post-test); #P < 0.05 SD vs WKY of the same treatment (Šidák post-test).

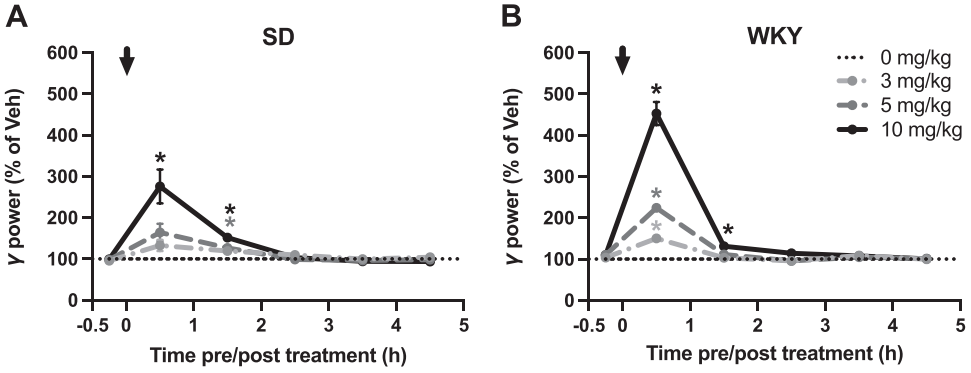

Fig. 5. The ketamine-induced increase in EEG gamma power is nearly twice as high in WKY rats than in SD rats. The time course of changes in EEG gamma power are shown in SD (A) and WKY rats (B) during the first 5 h after treatment with vehicle (0 mg/kg, s.c.) or ketamine (3, 5 and 10 mg/kg; s.c.). Data are presented as mean ± SEM. *P < 0.05 vs vehicle treatment (Dunnett post-test).

diminishes after repeated administration of the drug [32]. Therefore, it has been proposed that acute REM sleep suppression may predict the therapeutic efficacy of antidepressant drugs [36–40]. In this study, WKY rats showed an increased amount of baseline REM sleep compared to SD rats. A similarly increased amount of REM sleep has been shown in WKY rats compared to SD and Wistar rats previously [24,25]. Acute treatment

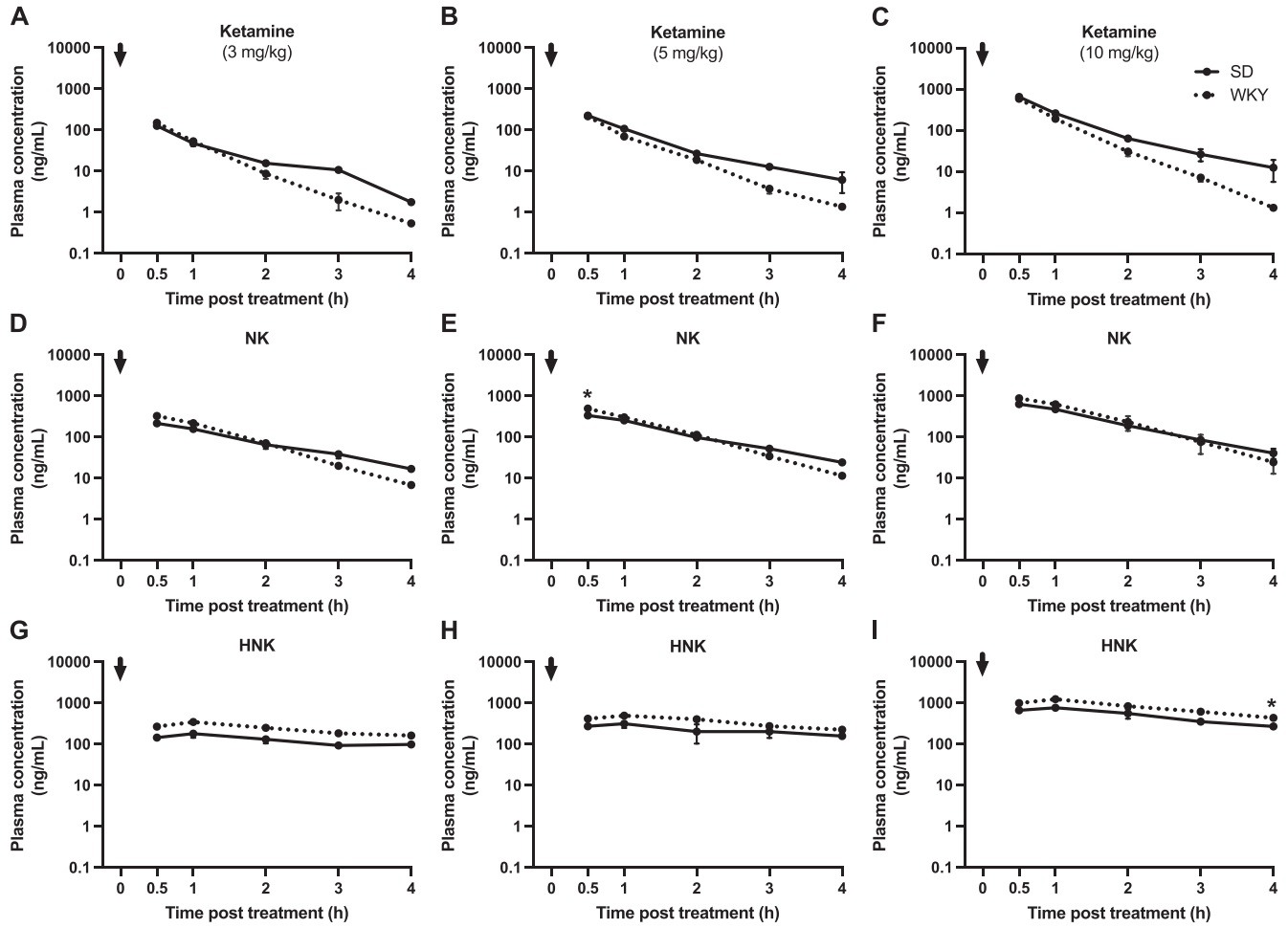

Fig. 6. The pharmacokinetics profile of ketamine and its metabolites is similar between SD and WKY rats. The time course of changes in the plasma concentration of ketamine (A, B, C), norketamine (NK; D, E, F) and hydroxynorketamine (HNK; G, H, I) are shown in SD (solid line) and WKY (dotted line) rats after treatment with ketamine (3, 5 and 10 mg/kg; s.c.). Data are presented as mean ± SEM. *P < 0.05 SD vs WKY of the same treatment (Šidák post-test).

with antidepressants (including ketamine) inhibits REM sleep in both SD and Wistar rats as we have shown here and others demonstrated previously [25,41,42]. Similarly, ketamine reduces the amount of REM sleep in patients with severe burns, but interestingly, increases it in MDD patients [43,44]. WKY rats are less sensitive to the suppression of REM sleep by serotonin reuptake inhibitors or tricyclic antidepressants than SD or WKY rats [25,41]. Subanaesthetic doses of ketamine, however, effectively supressed REM sleep in WKY rats during the first 3–4 h post-treatment in this study that may indicate antidepressant-like properties of the drug in a rodent model of TRD. Indeed, ketamine's antidepressant-like effect has been demonstrated in the forced swim test, learned helplessness and sucrose preference test in WKY rats previously [28,29,45]. Therefore, these data together with our results further support the predictive validity of acute REM sleep suppression as an index of antidepressant-like efficacy in TRD.

Although the precise mechanism through which subanaesthetic doses of ketamine suppresses REM sleep is not known, most likely this is achieved by acting on NMDA receptors expressed in neurons of the brain stem. It is well established that REM sleep is generated in the brain stem by the interaction between the glutamatergic neurons of pontine reticular formation (PRF) and cholinergic neurons of laterodorsal/pedunculopontine tegmental (LDT/PPT) nuclei [46]. Accordingly, injection of muscarinic receptor agonists into PRF induces REM sleep [47]. Similarly, low doses of glutamate injected into PPT increase REM sleep, but high doses of it increase wakefulness presumably through different mechanisms [48,49]. Furthermore, systemic administration of ketamine reduces acetylcholine release in the PRF [50]. Therefore, it seems most likely that the subanaesthetic doses of ketamine supressed REM sleep in this study by indirectly reducing the cholinergic tone in the PRF.

Subanaesthetic doses of ketamine reduce the symptoms of depression within hours after the treatment, and the antidepressant effects may last three to seven days in TRD patients [8–10]. This acute antidepressant effect of ketamine, however, can be extended for up to 6 weeks with repeat doses [51–53]. Given its short half-life (~45 min), ketamine's sustained antidepressant efficacy, however, cannot simply be attributed to the acute changes induced by the drug. A growing body of evidence suggests that the sustained antidepressant effects of ketamine are achieved by reversing the glutamatergic and GABAergic dysfunction found in patients with depression [10,12–14]. It has been suggested that ketamine increases glutamate neurotransmission in the prefrontal cortex by blocking the NMDA receptors on GABAergic neurons, which leads to increased synaptic plasticity through downstream molecular cascades and long-term changes in neural circuits [54,55].

Both clinical and pre-clinical studies have demonstrated that acute treatment with subanaesthetic doses of ketamine and with its metabolite, HNK, induces robust increase in EEG gamma power and rapid antidepressant effects in TRD, but the potential causal relationship between the two has not been fully explored yet [56–61]. Although the acute increase in gamma oscillations is primarily linked to the transient dissociative and psychotomimetic effects of ketamine [62,63], the gamma increase is also viewed as a potential marker of synaptic potentiation and neural network adaptation, which are necessary to

develop the sustained antidepressant effects of ketamine [64,65]. Gamma oscillations are primarily generated by networks of glutamatergic and gamma aminobutyric acid (GABA)-ergic interneurons of the cortex and controlled by cortically projecting GABA-ergic neurons of the basal forebrain [66]. Numerous studies found alterations in gamma oscillations in both MDD and bipolar disorder [67–74]. Although the functional significance of gamma power increase in the antidepressant effect of ketamine is unknown, depressed patients with lower baseline gamma power levels have better antidepressant responses if they also have a large increase in gamma power after ketamine treatment [75]. WKY rats show reduced EEG gamma power at REM sleep transitions and decreased gamma coherence between brain regions implicated in depression that is normalized by ketamine [76,77]. In our study, the baseline EEG gamma power was similar in SD and WKY rats during wakefulness and NREM sleep. However, the ketamine-induced increase in EEG gamma power was almost twice as high in WKY rats as in SD rats. Since the plasma concentrations of ketamine and its metabolites were similar between both strains, it is unlikely that the eminent increase in EEG gamma oscillations was due to altered ketamine metabolism in WKY rats. Thus, we hypothesize that the larger increases in gamma power could indicate an enhanced antidepressant-like response to ketamine in the WKY strain.

Apart from REM sleep and EEG gamm power alterations, depressed patients also have frequent nocturnal awakenings resulting in fragmentated sleep and poor sleep efficiency [78]. In our study, WKY rats had fragmented NREM sleep as shown by the shorter and increased number of NREM sleep bouts compared to SD rats. WKY rats also had increased EEG delta power during NREM sleep compared to SD rats that could reflect an increased propensity for sleep resulting from frequent awakenings [79]. However, apart from decreasing the number of NREM sleep bouts, ketamine had no effect on either EEG delta power or NREM sleep bout durations in WKY rats. This suggests that ketamine and its analogues may not address all aspects of disordered sleep in depression, and that additional treatment may be required. This is particularly important as untreated sleep disturbances are seen as risk factors for developing depression or relapse [80].

5. Conclusions

We show for the first time that the increased amount of REM sleep in WKY rats is supressed by subanaesthetic doses of ketamine, and this could be indicative of antidepressant-like efficacy of the drug in TRD. Although ketamine efficiently supresses REM sleep, it can only partially correct the fragmented NREM sleep seen in WKY rats suggesting that an adjuvant therapy may be required to address all aspects of the disrupted sleep seen in depression. Furthermore, we show that subanaesthetic doses of ketamine induce a more robust increase in EEG gamma power in WKY rats than in SD rats that is unlikely to be caused by strain-specific differences in ketamine metabolism. This eminent increase in EEG gamma oscillations may suggest an enhanced antidepressant response to ketamine in WKY rats. Thus, the ketamine-induced changes in sleep and EEG in WKY rats shown here may serve as key translational tools in an effort to discover novel therapeutics against TRD.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

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