Chronic administration of antipsychotics attenuates ongoing and ketamine-induced increases in cortical γ oscillations

Paul M. Anderson1,2, Didier Pinault2, Terence J. O’Brien1 and Nigel C. Jones1

1 Department of Medicine, Faculty of Medicine Dentistry and Health Sciences, University of Melbourne, Parkville 3010, Victoria, Australia
2 INSERM U1114, Neuropsychologie cognitive et physiopathologie de la schizophrénie, Université de Strasbourg, Fédération de Médecine Translationnelle de Strasbourg, 11 rue Humann, F-67085 Strasbourg, France

Abstract

Noncompetitive N-methyl-D-aspartate receptor (NMDAr) antagonists can elicit many of the symptoms observed in schizophrenia in healthy humans, and induce a behavioural phenotype in animals relevant to psychosis. These compounds also elevate the power and synchrony of gamma (γ) frequency (30–80 Hz) neural oscillations. Acute doses of antipsychotic medications have been shown to reduce ongoing γ power and to inhibit NMDAr antagonist-mediated psychosis-like behaviour in rodents. This study aimed to investigate how a chronic antipsychotic dosing regimen affects ongoing cortical γ oscillations, and the electrophysiological and behavioural responses induced by the NMDAr antagonist ketamine. Male Wistar rats were chronically treated with haloperidol (0.25 mg/kg/d), clozapine (5 mg/kg/d), LY379268 (0.3 mg/kg/d) or vehicle for 28 d, delivered by subcutaneous (s.c.) osmotic pumps. Weekly electrocorticogram (ECoG) recordings were acquired. On day 26, ketamine (5 mg/kg, s.c.) was administered, and ECoG and locomotor activity were simultaneously measured. These results were compared with data generated previously following acute treatment with these antipsychotics. Sustained and significant decreases in ongoing γ power were observed during chronic administration of haloperidol (64%) or clozapine (43%), but not of LY379268 (2% increase), compared with vehicle. Acute ketamine injection concurrently increased γ power and locomotor activity in vehicle-treated rats, and these effects were attenuated in rats chronically treated with all three antipsychotics. The ability of haloperidol or clozapine to inhibit ketamine-induced elevation in γ power was not observed following acute administration of these drugs. These results indicate that modulation of γ power may be a useful biomarker of chronic antipsychotic efficacy.

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Introduction

Schizophrenia is a debilitating psychiatric disorder that is characterized by a range of symptoms, including hallucinations, delusions, emotional disturbances and diverse cognitive deficits (Harrison, 1999). In recent years there has been a convergence of various lines of evidence suggesting that the underlying pathophysiology of schizophrenia involves disruptions of neural synchrony (Uhlhaas et al., 2008). In particular, it has been demonstrated that gamma (γ) frequency (30–80 Hz) oscillations are disrupted in patients with schizophrenia. These disruptions appear to be complex, with studies reporting both decreases in stimulus-evoked γ oscillations (Kwon et al., 1999; Spencer et al., 2003; Ford and Roth, 2004), as well as increases in ongoing γ oscillations (typically associated with psychotic events or positive symptoms) (Baldeweg et al., 1998; Gordon et al., 2001; Becker et al., 2009; Spencer et al., 2009; Behrendt, 2010). The functional role of γ oscillations has been linked to a range of higher-order brain functions, including cognition (Engel et al., 2001), working-memory (Tallon-Baudry et al., 1998; Howard et al., 2003; Uhlhaas et al., 2008) and sensory perception (Lee et al., 2003; Spencer et al., 2004; Herrmann and Demiralp, 2005; Light et al., 2006; Uhlhaas et al., 2006; Gross et al., 2007; Krishnan et al., 2009; Maharajh et al., 2010). These same cognitive processes are disrupted in schizophrenia, suggesting that aberrant γ oscillations may be directly related to the pathophysiology of the disorder, although proving causation of this is challenging.

Ketamine is a dissociative anaesthetic drug and a non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptors. Although it has been shown to have a broad...
pharmacological profile, including interactions at dopamine and serotonin receptors (Kapur and Seeman, 2002), it is principally regarded as an NMDA receptor ligand. Ketamine and other NMDA receptor (NMDAr) antagonists have been shown to induce hallucinations in healthy humans, and exacerbate psychotic symptoms in schizophrenic patients (Krystal et al., 1994). Subsequent studies described the ability of ketamine to promote affective symptoms and cognitive deficits (Hetem et al., 2000; Stone et al., 2008; Driesen et al., 2013), and some suggest that ketamine more closely models negative and cognitive symptoms of schizophrenia (Newcomer et al., 1999). Acute ketamine administration is hence widely considered to be a valid model of the positive, negative and cognitive symptoms of schizophrenia hence widely considered to be a valid model of the positive, negative and cognitive symptoms of schizophrenia (Frohlich and Van Horn, 2014). This and other evidence has led to the development of the NMDAr hypofunction hypothesis of schizophrenia, which posits that reduced activity at NMDA receptors leads to the expression of schizophrenia symptoms. We (Pinault, 2008; Hakami et al., 2009) and others (Ehrlichman et al., 2009; Lazarewicz et al., 2010) previously demonstrated that NMDAr antagonists dose-dependently increase the power of ongoing γ cortical oscillations in rodents and also recapitulate complex electrophysiological abnormalities seen in schizophrenia (Kulikova et al., 2012; Saunders et al., 2012). We further developed this model by examining the effects of antipsychotic compounds on ongoing γ oscillations, and in response to a ketamine challenge (Jones et al., 2012). We tested a typical (haloperidol) and atypical (clozapine) antipsychotic and a preclinical metabotropic glutamate 2/3 receptor (mGluR2/3) agonist (LY379268) with antipsychotic properties (Imre, 2007). Our results demonstrated that, on their own, antipsychotic medications reduce the power of ongoing cortical γ oscillations in freely moving rodents. Antipsychotics also reduce oscillations of higher frequencies (100–180 Hz) in the nucleus accumbens (Olszewski et al., 2013). However, acute treatment with conventional antipsychotics did not impact the ability of ketamine to increase γ oscillations, a finding in contrast to the effects of these drugs on ketamine-induced hyperlocomotor activity (Jones et al., 2012). The effect of antipsychotics to modulate γ oscillations may confound much of the literature examining these neural rhythms which has been generated in clinical populations. Although some studies have compared drug-free and medicated patients (Gallinat et al., 2004), or examined first episode patients to eliminate the effects of medication (Symond et al., 2005), the vast majority do not control for drug effects. This therefore remains an understudied area with important clinical implications.

Given the widespread reports of γ frequency alterations in schizophrenia, the ability of antipsychotic medications to modulate neuronal oscillations may be central to their efficacy, with the potency of modulation of γ activity representing a potential new biomarker of antipsychotic efficacy. Previous studies have only examined acute antipsychotic drug treatment, whereas in clinical situations, the efficacy of these drugs typically take several weeks of administration to manifest (Gelder et al., 2000). This study aims to examine the effect of chronic antipsychotic administration on ongoing and on the acute challenge of low-dose ketamine-induced increases in γ oscillations.

Materials and methods

Animals

Male Wistar rats aged 10–12 wk old (weighing 250–350 g) were used (total n=44). Animals were bred and housed (3–4 per cage) in the Biological Research Facility of the Department of Medicine, Royal Melbourne Hospital, University of Melbourne. Animals had access to food and water ad libitum and were kept on a 12 h light–dark cycle (lights on at 06:00 hours). All experiments were approved by the University of Melbourne Animal Ethics committee (Ethics #1011868) and adhered to the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes.

Surgery

Animals were anaesthetised by inhalation of isoflurane (5% induction, 1.5–2.5% maintenance) in equal parts of medical air and oxygen and implanted with an osmotic mini-pump (Model 2ML4, Alzet, USA) in the dorsal thoracic region by way of a single incision midway between the scapulae. Animals were then positioned in a stereotaxic frame as described previously (Hakami et al., 2009) for implantation of electrocorticograph (ECoG) electrodes. Briefly, a single midline incision was made over the scalp and six holes were drilled through the skull with stereotaxic guidance (Paxinos and Watson, 1998) [2 mm anterior and 2 mm lateral to bregma bilaterally (active electrodes); 2 mm posterior and 2 mm lateral to bregma bilaterally (ground electrodes); and 2 mm posterior and 2 mm lateral to lambda bilaterally (reference electrodes)]. Electrodes were then screwed into the skull without breaching the dura, and dental cement applied to the skull to fix the electrodes in place. After recovery from anaesthesia, animals were housed in separate cages for the duration of the experiment.

Drugs and vehicles

Clozapine, haloperidol and LY379268 were obtained from Tocris Bioscience (UK). Ketamine was obtained from Parnell Laboratories (Australia). Isoflurane was purchased from Abbott Pharmaceuticals (USA). Haloperidol and ketamine were diluted in 0.9% sterile saline, clozapine was dissolved in 10% acetic acid in sterile water with pH adjusted to 6.0 using 10 M NaOH. Control
pumps were loaded with 10% acetic acid (n=5) or sterile saline (n=3): there were no significant differences in the outcome of these treatments so the two vehicle control conditions were combined for analysis. Pumps were weighed before and after filling, and residual volume was checked at the end of the experiment to ensure adequate delivery (>95% expected volume) of drug. Clozapine was administered to give an approximate dose of 5 mg/kg/d, haloperidol at 0.25 mg/kg/d and LY 79268 at 0.3 mg/kg/d, based on the predicted weight of animals at day 28. Dosages were selected on two criteria: to maintain a clinically relevant plasma concentration (for haloperidol and clozapine) (Kapur et al., 2003) and to have an equivalent effect on γ power (based on acute dosing (Jones et al., 2012)).

Assessment of ECoG power and locomotor activity

Animals underwent ‘baseline’ ECoG recordings at 7, 14 and 21 d post-surgery. Animals had a recording cable attached while in their home cages and after a 30 min acclimatisation period, 30 min of ECoG activity was recorded. On day 26 or 27 of the experiment animals underwent a ketamine ‘challenge’. Animals were brought into the Behavioural Testing Facility in the Department of Medicine at least 30 min before the start of the study to allow habituation to the environment. Rats were then individually placed into an open arena (1 m diameter), while attached to an ECoG recording cable suspended from the ceiling. Each rat was allowed to acclimatise to the arena for 30 min at which point ECoG recording began. Following a 30 min baseline recording animals received an injection of ketamine (5 mg/kg s.c.) and recorded for another 60 min. Throughout the ECoG acquisition animals’ locomotor activity was video-tracked and objectively assessed with EthoVision software (Noldus, The Netherlands), total distance travelled was calculated for each 2 min interval.

ECoG acquisition and analysis

ECoG was acquired and analysed with a Synamp amplifier and SCAN v4.5 software (Compumedics, Australia). ECoG was sampled at 2000 Hz with a band-pass of 0.5–1000 Hz. Drug effects on the power of different frequency bands was assessed as previously described (Hakami et al., 2009). Briefly, raw ECoG was sectioned into 2.048 s epochs, fast Fourier transformations were performed to determine the average power in different frequency bands (δ – 1–4 Hz; θ – 4–8 Hz; α – 8–12 Hz; β – 13–30; γ – 30–80 Hz) and average power was then calculated for each 2 min interval and averaged over 30 min. For the ketamine challenge experiments, to quantify both γ power and locomotor activity, the first 15 data points (representing the 30 min prior to ketamine) are averaged to give a baseline activity for each recording, all recorded values are then expressed as percentage of this activity.

Acute dosage experiment

Data generated from our previous acute dosage study (Jones et al., 2012) were reanalysed here to directly compare the effects of different dosage paradigms (i.e. acute vs. chronic). ECoG data from the acute experiment were acquired with a MacLab amplifier and Chart v. 3.5 software (AD Instruments, Australia). 50 Hz line noise was detected and digitally subtracted from the recording in real time using selective eliminators (Humbug noise eliminators; Digitimer, UK) which do not affect the biological signal. Single doses of clozapine (5 mg/kg), haloperidol (0.25 mg/kg) and LY379268 (0.3 mg/kg) and ketamine (5 mg/kg) were used. ECoG and locomotor data were acquired in the same behavioural facility using a protocol similar to the ketamine ‘challenge’ recording: first a 30 min acclimatisation period in the arena, followed by 30 min baseline recordings. This was followed by s.c. injection of antipsychotic and 30 min post antipsychotic recording, followed by injection of ketamine and 60 min recording. Electrophysiology data from the acute experiment were expressed as a percentage of the post-antipsychotic period average.

Statistical analyses

Differences between treatment groups in spectral power were assessed by averaging the 15 data points from the 30 min baseline recording and then comparing these values using the Kruskal–Wallis test, with Dunn’s multiple comparisons post-hoc test. Both the electrophysiological and locomotor response to ketamine challenge was assessed with two-way analysis of variance (ANOVA) with repeated measures (time) comparing drug treatment to vehicle controls. The effects of ketamine on γ power were quantified by analysing the area under the curve for each animal, normalised to the mean γ power in the 20 min preceding ketamine injection. Comparisons between acute and chronic treatments were made with two-way ANOVA, with Bonferroni’s post-hoc test comparing treatments within a treatment regime.

Results

Haloperidol and clozapine stably reduce the power of ongoing γ oscillations, while chronic LY379268 increases low frequency power

Chronic treatment with the conventional antipsychotics haloperidol and clozapine caused pronounced and persistent decreases across the power spectrum (Fig. 1a). Conversely LY379268-treated animals displayed power comparable to vehicle-treated animals. These changes were stable over the 4-wk experimental period with the decrease in θ, α and γ power caused by clozapine and haloperidol persisting throughout. Robust differences
were observed in the $\gamma$ frequency band, two-way repeated measures ANOVA showed a significant effect of drug treatment ($F_{(3,105)}=11.92, p<0.0001$). Post-hoc tests showed significant differences between haloperidol- and vehicle-treated animals at all time points ($p<0.01$), while clozapine was different to vehicle at all but week 2 ($p<0.05$). LY379268-treated animals did not have significantly different $\gamma$ power at any time-point. Theta and alpha power bands were also shown to be altered by antipsychotic treatment (two-way repeated measures ANOVA, theta: $F_{(3,105)}=3.161, p=0.036$, alpha: $F_{(3,105)}=8.696, p=0.0002$), while beta was not $F_{(3,105)}=0.706, p=0.555$. No effects of the drugs were observed in the delta frequency band (all $p>0.05$).
Chronic treatment with haloperidol or clozapine significantly attenuates the ketamine-induced rise in \( \gamma \) power, but acute treatment does not.

The electrophysiological response to the ketamine challenge injection (5 mg/kg s.c.) manifested as a rapid and large increase in the power of ongoing \( \gamma \) oscillations, with vehicle-treated animals having an average maximum response of 237±14% relative to baseline occurring at 10 min post-injection. This effect of ketamine was inhibited in the chronically treated animals, with all treatments reducing ketamine’s effect. In the clozapine- and LY379268-treated animals, the power of ongoing \( \gamma \) oscillations returned to baseline levels sooner than vehicle-treated animals (Fig. 2a). Peak responses for the three treatment groups were haloperidol: 187±13% occurring at 10 min post-injection; clozapine: 213±9% at 10 min post injection; and LY379268: 177±7% at 12 min post injection. ANOVA showed that treatment had a statistically significant effect on \( \gamma \) power for haloperidol \((F_{(1,20)}=6.57, \ p=0.0185)\), clozapine \((F_{(1,24)}=25.30, \ p<0.0001)\) and LY379268 \((F_{(1,22)}=37.83, \ p<0.0001)\). Ketamine did not affect...
oscillations in the other frequency bands, and so no further analyses were conducted on these.

In order to compare the effects of chronic treatment with antipsychotic drugs to those induced by a single acute dose, we reanalysed our previously published data (Jones et al., 2012), examining single acute doses of the same drugs. When comparing the time course of effects of acute antipsychotics, only LY379268 significantly reduced the electrophysiological effect of ketamine \((F_{1.24} = 52.68, p < 0.0001)\) compared with vehicle-treated animals (Fig. 2b). The electrophysiological response to ketamine was quantified by calculating the area under the curve 0–60 min post ketamine injection (Fig. 2c), and responses compared between the acute and chronic treatment paradigms. ANOVA showed that drug treatment \((p < 0.0001)\) and treatment regime \((p < 0.0001)\) were significantly different, and that there was a significant interaction between these variables \((p = 0.0032)\). Bonferroni post-hoc tests showed that for chronic treatment, all three antipsychotics significantly reduced the effect of ketamine on \(\gamma\) power \((p < 0.05)\), whereas for acute treatment, LY379268 was the only drug to significantly affect this outcome \((p < 0.001)\). As such, there was a differential effect of haloperidol and clozapine, such that they were only effective when chronically administered.

**All three antipsychotics attenuate ketamine-induced hyper-locomotion**

The effects of chronic antipsychotic treatment on the power of ongoing \(\gamma\) oscillations were mirrored in the outcome of the locomotor response to ketamine injection. Ketamine caused a hyperlocomotor response in all injected animals; in vehicle-treated animals, we observed a maximum response of 932±229% occurring at 2 min post injection (Fig. 3a). This response was significantly, but not completely, reduced in all three chronic treatment groups with maximum locomotor activities for haloperidol: 441±92% at 8 min post-injection, clozapine: 494±151% at 2 min and LY379268: 313±105% at 2 min post injection. ANOVA showed that chronic treatment had a significant effect on the locomotor response for haloperidol \((F_{1.13} = 4.69, p = 0.0496)\), clozapine \((F_{1.14} = 8.28, p = 0.0122)\) and LY379268 \((F_{1.12} = 9.96, p = 0.0083)\). Acute treatment (Fig. 3b) evoked similar results, with haloperidol \((F_{1.14} = 22.29, p = 0.0003)\), clozapine \((F_{1.13} = 8.12, p = 0.0137)\) and LY379268 \((F_{1.13} = 5.68, p = 0.0362)\) all significantly inhibiting the locomotor response of ketamine as compared with vehicle-treated animals.

In contrast to their effects on the electrophysiological response to ketamine, when assessing the area under the curve (Fig. 3c), there were no differences between the acute and chronic treatment regime \((p > 0.05)\), such that all treatments were equally effective at reducing the locomotor response to ketamine.

**Discussion**

The primary finding of this study is that chronic treatment with the antipsychotic medications haloperidol and clozapine, and the pre-clinical drug LY379268, attenuate the effects of an acute ketamine challenge, as measured by electrophysiological and behavioural responses. Chronic treatment with haloperidol and clozapine attenuated the ketamine-induced increase in \(\gamma\) power, an effect not seen with single acute dosages. The mGluR2/3 agonist LY379268 reduced ketamine-induced locomotor and \(\gamma\) hyper-activities under both acute and chronic treatment paradigms. Furthermore LY379268 did not alter the power of ongoing physiological \(\gamma\) oscillations during the 4-wk treatment, whereas the conventional antipsychotics, clozapine and haloperidol, caused a pronounced depression of the ongoing background \(\gamma\) activity that was sustained throughout the treatment period.

The observation that chronic treatment for 4 wk with the conventional antipsychotics was effective in attenuating the effects of ketamine to increase cerebral \(\gamma\) activity, while acute single dosing was not (Jones et al., 2012), is potentially important finding. In clinical practice, the efficacy of antipsychotic treatment is typically not seen until 2–3 weeks after treatment has been instituted (Gelder et al., 2000). Although some recent studies have questioned this (Agid et al., 2003), it is clear that in clinical settings antipsychotic treatment displays increasing efficacy over time. The findings of this study suggest that the cerebral \(\gamma\) activity response to ketamine may represent an endophenotype of the efficacy of chronic antipsychotic treatment which is practical for use in drug screening in animal models.

There is a large body of evidence reporting altered \(\gamma\) frequency oscillations in patients with schizophrenia, with studies generally, but not exclusively, reporting both decreases in evoked \(\gamma\) oscillations (potentially related to the negative symptoms of schizophrenia) and increases in ongoing \(\gamma\) oscillations (correlating with positive signs), as mentioned in the introduction. It has been proposed that these findings represent different aspects of an overall disruption in \(\gamma\) signal-to-noise in cortical information processing (Gallinat et al., 2004; Flynn et al., 2008; Krishnan et al., 2009; Williams et al., 2009); and see (Gandal et al., 2012) for review). This conceptualises that the increase in ongoing \(\gamma\) power triggered by NMDAr antagonists represent a diffuse network noise, disrupting cortical processing and leading to perceptual and cognitive deficits reminiscent of those seen in schizophrenia. The findings of this study support the proposition that modulation of \(\gamma\) power represents a key property of antipsychotic medications, with both clozapine and haloperidol’s capacity to inhibit aberrant \(\gamma\) oscillations potentially reflecting their efficacy against positive symptoms.

The differential effects of LY379268 on spontaneous (ongoing) \(\gamma\) activity compared with the established
clinical antipsychotic drugs, haloperidol and clozapine, is noteworthy. LY379268 is a mGluR2/3 agonist, while most clinical antipsychotic drugs are thought to primarily act via dopamine D2 receptors (although clozapine has less effects at this receptor than haloperidol) (Seeman, 2002). The mGluR2/3 agonists have been shown to decrease the release of glutamate and inhibit excitatory synaptic activity (Lovinger and McCool, 1995; Yoshino et al., 1996; Battaglia et al., 1997). Ketamine (and other NMDAr antagonists) trigger release of glutamate in the pre-frontal cortex (Adams and Moghaddam, 1998) and LY379268 pre-treatment can block this glutamate release following PCP administration (Lorrain et al., 2003), providing a plausible mechanism of action of how this drug may combat the behavioural and electrophysiological effects of ketamine observed here. Furthermore, although LY379268 causes a transient decrease in ongoing $\gamma$ power following acute administration (Jones et al., 2012), this effect was not seen with chronic treatment. In contrast the two clinical antipsychotic drugs resulted in sustained decreases in ongoing $\gamma$ activity. mGluR2/3 receptor agonists have been shown in clinical trials to have a lower cognitive side effect profile (Adams et al., 2013). It is possible that the lack of effect of LY379268 on the

Fig. 3. Effects of antipsychotic treatment on ketamine-induced locomotion. Chronic treatment (a) with all three different drugs attenuated the ketamine-induced locomotor activity as compared with vehicle treatment. Similar effects on locomotion where seen with acutely treated animals (b) where all three medications attenuated the hyperlocomotion effects of ketamine. For all drugs, these two treatment regimens were equally effective at reducing the ketamine-induced locomotor effect (c). Data represent mean±s.e.m, n=6–8/group. * indicates p<0.05 compared with vehicle within the same treatment regime (i.e. acute or chronic). AUC: area under curve.
physiological ongoing $\gamma$ may be related to its reduced cognitive side effects, given the role they are thought to play on cognitive processing. Haloperidol has been shown to induce negative symptoms (Veselinovic et al., 2013), and a comprehensive assessment in healthy subjects showed a general effect of impairing attention and speed of processing caused by antipsychotic administration (Ramaekers et al., 1999).

It is important to point out that our study was conducted in healthy animals, displaying physiologically normal $\gamma$ oscillations, not the chronic pathological abnormalities seen in schizophrenia. This limits any interpretations made, with the acute NMDA receptor antagonist treatment considered an acute psychotic precipitant. Further work performed in genetic or chronic pharmacological models for the schizophrenic state should be conducted to validate the relevance of the findings of this study. Nonetheless, the findings of this study – that chronic treatment with antipsychotic medications attenuates the ketamine-induced increase in $\gamma$ power – supports the hypothesis that $\gamma$ frequency abnormalities are a significant feature of the psychotic-like state that is induced in the NMDAr model. In addition, our studies do not contain a placebo injection arm as a control to the ketamine injections. Our previous work has demonstrated that injection of vehicle treatments can impact ongoing $\gamma$ power, but this is minimal and short-lived (<2 min), and dwarfed by the effect of ketamine (Hakami et al., 2009). Although we should consider the potential of a placebo effect here, our primary comparisons are the inhibition of the effect of ketamine to increase $\gamma$ frequency power by antipsychotic drugs, so the lack of placebo for ketamine should not compromise the interpretation of the data in this regard.

In conclusion this study has demonstrated chronic antipsychotic administration causes a strong attenuation of the behavioural and electrophysiological effects of ketamine, as assessed through hyperlocomotion and ECoG $\gamma$ hyperactivity. The modulation of $\gamma$ frequency oscillations by NMDA receptor antagonists and antipsychotic medications provide insights into the role that $\gamma$ frequency abnormalities may play in schizophrenia, and have potential utility as a measure of antipsychotic efficacy and cognitive side effects.

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Chronic antipsychotics modulate $\gamma$ oscillations 1903


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