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Examination of Cognitive Deficits Produced by Sub-Chronic Ketamine Exposure in Rats

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Abstract: ***Chronic NMDA receptor suppression by NMDA antagonists (ketamine), induce structural changes in neocortical and limbic brain regions, resulting in similar cognitive deficits to that observed clinically in schizophrenia. Objectives: This study was designed to evaluate cognitive deficits following ketamine administration in rodents, assessed through an attentional set-shifting paradigm. Thus, allowing evaluation of cognitive flexibility in the form of discrimination acquisition, reversal learning and intra/extra-dimensional shifts (ability to switch between dimensions). Methods: Forty four male Lister Hooded rats, underwent a five day daily sub-chronic treatment regime prior to habituation. The three treatment groups where; VEH, ketamine (10mg/kg, IP) and ketamine (30mg/kg, IP). Rats underwent habituation two days post treatment cessation, consisting of a simple odour and medium discrimination. 24 Hours later, rats were assessed on a attentional set shifting task. Results: Sub-chronic ketamine treatment impaired reversal learning in a dose dependent manner. Animals treated with ketamine (30mg/kg), required significantly more trials to criterion for all three reversal trials (REV1-3). Ketamine (10mg/kg) treatment significantly impaired acquisition during REV2. Ketamine (30mg/kg) treated rats made significantly more errors during each reversal (REV1-3). A clear trend emerged between ketamine exposure and latency; rats treated with ketamine (30mg/kg) required longer to complete REV1 to EDS. Ketamine (30mg/kg) treatment resulted in a significant deficit in the acquisition of the odour and medium tasks, during habituation. Conclusion: These results show sub-chronic ketamine treatment impairs reversal learning. Our findings support the impairments observed clinically following CANTAB assessment in schizophrenic patients. Hence, our data suggests sub-chronic ketamine treatment results in similar cognitive deficits. Our results support the hypothesis that ketamine is an important pharmacological compound to model cognitive deficits in rats.***

Keywords: Schizophrenia, Chronic Ketamine, Set-shifting, Rat

1. Introduction

The notion suggesting chemical dysfunction may be related to the pathophysiology of schizophrenia has been around since the late 19th century (1), but it wasn't until the 1960s when the dopamine hypothesis was born from two distinct clinical observations. Conell et al. observed the similarity between amphetamine induced psychosis and acute paranoid schizophrenia (2), which could be improved following neuroleptic administration (3). The dopamine hypothesis suggests the etiology of schizophrenia was due to the overactivation of the mesolimbic dopaminergic pathway, which projects from the VTA to the PFC(4).

The glutamate hypothesis followed, as proposed by Kim et al. postulating NMDA receptor (NMDAR) hypofunction mediates psychosis (5). This theory was elucidated by a simple observation that schizophrenic patients had low CSF glutamate levels. Over the past ten years the glutamate hypothesis has been updated to incorporate dopamine, to propose cortical glutamatergic projections module the firing of sub-cortical DA neurones. The integrated hypothesis suggests the cognitive symptoms are due to hypoactivation of the mesolimbic dopaminergic pathway to the dorsolateral prefrontal cortex (DLPFC) by the descending cortico-brain stem glutamate projection. Conversely, the positive symptoms are associated with reduced glutamatergic activation of the GABA interneurons in the ventral tagmental area (VTA), resulting in the disinhibition and subsequent overactivation of the mesolimibic dopaminergic pathway.

The clinical implications associated with NMDA antagonists (ketamine, PCP) administration in humans are well documented. Acute ketamine administration to healthy volunteers mediates a range of symptoms associated with schizophrenia (positive, negative and cognitive impairments), in a dose dependant manner (6-8). Whilst ketamine administration to schizophrenic patients results in exacerbation of psychotic and cognitive symptoms (9). On the contrary, compounds which enhance NMDAR function have been shown to improve symptoms in schizophrenic patients. Pharmacological compounds used to induce the symptoms of schizophrenia in rodents and primates include; DA agonist (e.g. amphetamine) and NMDA antagonists (e.g. ketamine) (10-13), PCP (14), Dizocilpine or MK-801 (15, 16). In contrast to NMDA antagonist which model the range of symptoms observed in schizophrenia, dopamine agonist-like amphetamine reflects only the positive symptoms (17). Neurochemical alterations associated with acute ketamine administration include; reduced GABA release (18), increased DA release into the PFC and nucleus accumbens and increased glutamate in the PFC (19, 20). The chronic effects include, reduced dopamine production and consumption in the prefrontal cortex (largely the medial frontal cortex in rats) (21), reduced levels of extracellular glutamate in the frontal area (19) and reduced mRNA expression of essential enzymes (GAD67) required for GABA synthesis. In addition, acute exposure to ketamine inducers the expression of a gene Homer1a (candidate gene) within the ventral striatum and nucleus accumbens (22). C-fos and fos related antigen expression has also been detected in the cortical areas, nucleus accumbens and amygdala (23).

Keilhoff et al. reported the target site for ketamine was located in denate gyrus (hippocampus), due to restricted expression of the immediate early gene TXNF, C-fos, similar to acute expression (24), whilst other studies have detected immediate early gene expression within the posterior cingulate and retrosplenial cortex (25, 26). Deakin

et al. investigated the effects of acute ketamine administration by pharmacological magnetic resonance imaging (phMRI), reported OFC deactivation outlasted any other attenuation of the BOLD signal, furthermore, the deactivation of the subgenual cingulate and activation of the mid-posterior cingulate correlated with psychosis ratings (27). In addition PET studies in healthy volunteers following acute ketamine exposure, results in increased DA release in the striatum (28). In comparison to chronic NMDAR administration which results in reduced DA release.

The PFC has a long been identified as a critical site underlying attentional flexibility, with increasing evidence emerging that distinct areas with the PFC mediate different aspects of cognitive. The medial PFC is involved in higher processing (ED-shifts) (16) whilst the orbitofontal PFC (OFC) is more significant for less complex lower order tasks (reversal learning). Ragozzino et al. suggested the importance of the dorsomedial striatum within reversal learning due to interactions with the OFC, following tetracaine hydrochloride lesioning studies (29). The midline thalamic regions have projections to both the prefrontal cortex (30) and nucleus accumbens (NAc) (31). The NAc and midline thalamus (MDT) aid the effective completion of rewarded task, as they reduce inappropriate responses during the acquisition of novel strategies. Inactivation of the NAc shell or core prior to initial discrimination training, improved the outcome of the set-shifting task and impaired discrimination shifting, respectively (32). Disruption of the cortical thalamic interaction results in an increase in preservative errors, whilst inactivation of the projections between the PFC and NAc results in an increase in both preservative and regressive errors. In addition, inactivation of the NAc thalamic interaction had little effect on set-shifting. DA function within the PFC has been shown to be critical in set-shifting, as D1 (33) or D2 receptors inhibition, results in deficient set-shifting capability, whilst D4 antagonists improve set-shifting performance (34). In addition, metabotropic glutamate receptors (mGluRs) may also have a role in schizophrenia due to increased selective expression within the OFC (35).

The OFC is implicated in decision making and reward anticipation, with converging evidence suggesting OFC dysfunction is implicated in schizophrenia. Homayoun et al. reported NMDAR antagonists both increase the activity of pyramidal cell in the OFC but also inhibit the activity of inhibitory GABAergic interneuron's similar to that of amphetamine, corresponding to the hyperactivity associated with the OFC in individuals with schizophrenia. Furthermore, haloperidol clozapine, LY354740 and CDPPB normalised NMDA hyperactivity associated with NMDAR hypofunction (36). Ragozzino *et al.* injected a muscarinic antagonist (scopolamine) directly into the dorsomedial striatum. This resulted in an attenuated response during reversal learning (37). A subsequent experiment reported, Ach output increased during the acquisition of the task and subsequently normalised upon successful completion (38).

The ability to switch between attentional sets has been evaluation clinically, using the Wisconsin Card Sorting Task (WCST) (39). WCST assessment in schizophrenic patients has clearly identified significant set shifting deficits (40). In recent years the CANTAB test battery has been introduced, which includes updated version of the WCST and novel ID-ED tasks. These tests further confirm the inability of schizophrenics to flexibility adapt to changing dimensions. Birrell and Brown modified the original visual stimuli set-shifting paradigm for non-human primates and humans to olfactory and tactile stimuli (41). Thus, enabling the evaluation of different aspects of cognitive flexibility in rodents, these include; discrimination acquisition, reversal learning and intra/extra-dimensional shifts. Previous studies using this paradigm have largely focused on PCP.

Rats treated with PCP (42, 43) or sensitized to amphetamine show ID-ED deficits, in contrast to PCP sensitization which does not show attentional set shifting impairment (44). Direct excitotoxin infusion into the lateral PFC or OFC in primates, produced a deficits in set shifting and reversal learning respectfully (45). These results have been reflected in rodent studies, Lesioning of the medial PFC or OFC in deficiency in the ID-ED shift (41) and reversal learning (46), respectfully. The aim of this study is to determine the effects of sub-chronic ketamine administration on an attentional set-shifted paradigm, as described by Birrell and Brown (41).

2. Material and Methods

2.1 Animals

Forty four male Lister hooded rats (Harlan, Oxfordshire, UK), housed in pairs in (28X45 X13) Perspex cages (North Kent plastic cage company "RB3"). In temperature (21 ± 1 °C) and light controlled (12hr cycle) rooms. Behavioural testing occurred during the light phase from 0700 to 1900. Rats weighed between 240-320g, they were freely available to water but food restricted at ≥85% of their ad libitum weight (16-18g/day), with daily monitoring in respect to a standard growth curve. This study was carried out in accordance to the Animals (Scientific Procedures) Act, 1986 and its associated guidelines.

2.2 Compound preparation

(±)-Ketamine hydrochloride (SIGMA, UK) was dissolved in physiological saline (VEH) and pH balanced (pH5.2) to produce two concentrations of ketamine, 10mg/ml and 30mg/ml.

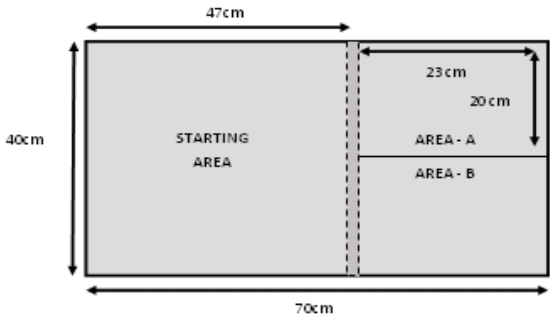

Figure 1: Plan of set-shifting testing box, divided into 3 sections, the dotted line indicates the removal removable Plexiglas divider, whilst the unbroken line, indicates a removable plastic panel separating area A and B.

2.3 Drug administration

Rats (n=44) were randomly designated into 3 groups; VEH+VEH 1ml/kg, VEH + ketamine- 1.0ml/kg, 10mg/ml and VEH + Ketamine 1.0ml/kg, 30mg/ml. The drugs were administered daily IP for 5 days, followed by a 2 day wash out period prior to habituation.

2.4 Apparatus

The testing equipment, was a modified plastic cage (approx. 40 X 70 X 18), with 1/3 being split into two compartments (by Plexiglass panels), which housed two ceramic bowls. Plastic panels could be inserted to prevent access to one or both compartment (Figure 1).

2.5 Habituation

The rats were first trained to dig in ceramic bowls (7cm diameter and 4cm depth) filled with coarse sawdust, containing half a Honey Nut Cheerior (HNC) (Nestle, Wirral, UK) as a reward. To complete the digging step, the rat must complete 6 consecutive retrievals from each bowl; the HNC was replaced following retrieval from both bowls. Next, the rats were exposed to simple odour discrimination (mint vs. oregano) in a course sawdust medium. This was followed by a medium discrimination (polystyrene vs. crinkled cardboard). The mint and polystyrene exemplar were rebated, upon successful retrieval. Each trial was initiated by a discovery trial, the dividers were raised, allowing access to both bowls, but only one contained the HNC. In the event the rat made an error (dug in the unbaited bowl) during the discovery period, the error was recorded, but the trial continued until the HNC was found. Following the four discovery trials, if the rat dug in the unbaited bowl, an error was recorded and the trial was terminated. Criterion was defined as six consecutive error free trials. Exemplars used throughout the habituation were not used during test. The rat was allowed to assess the bowl by smell, but a dig was defined by the disturbance of medium

Table 1

	Dimensions		Exemplar combinations	
Discrimination	**Relevant**	**Irrelevant**	**Correct**	**Incorrect**
Simple (SD)	Odour	Medium	**O1**	O2
Compound (CD)	Odour	Medium	**O1**/M1	O2/M1
			O1/M2	O2/M2
Reversal (Rev1)	Odour	Medium	**O2**/M1	O1/M1
			O2/M2	O1/M2
Intra-dimensional shift (IDS)	Odour	Medium	**O3**/M3	O4/M3
			O3/M4	O4/M4
Reversal (Rev2)	Odour	Medium	**O4**/M3	O3/M3
			O4/M4	O3/M4
Extradimensional shift (EDS)	Medium	Odour	**M5**/O5	M6/O5
			M5/O6	M6/O6
Reversal (Rev3)	Medium	Odour	**M6**/O5	M5/O5
			M6/O6	M5/O6

Table 1: Discrimination - The order of discriminations remained constant for each trial. The correct exemplars are shown in bold; the defined position within the set-shifting apparatus (Area-A/B) was determined by a prior pseudorandom sequence, thus preventing any possible sequence identification

2.6 Testing paradigm

The testing paradigm was initiated by four discovery trials; subsequent trials were terminated in the event the rat dug in the unbaited bowl (as stated above). During the testing period, the rats were exposed to seven discriminations (Table 1), the simple discrimination (SD) only differed by one dimensions (odour or medium).

The compound discrimination (CD), incorporated an extra dimension, however the correct exemplars remained constant from the previous SD. This was followed by a reversal (REV1), the dimensions and exemplars remained constant yet the correct stimuli from CD, was now incorrect. During the intra-dimensional shift (IDS), the dimension remained constant but with new exemplars, this was followed by a reversal (REV2) and then the extra-dimensional shift (EDS) where there was a complete change in dimension (odour to medium) and then a final reversal (REV3).

As olfactory and tactile stimuli were used, there were six possible paradigms (odour to medium or medium to odour). However, there was too many exemplars to allow full counterbalancing, therefore exemplars were always used in pairs (Table 1) (e.g. If paprika was the positive stimulus, thyme was the negative stimulus, vice versa). There were too many pairs to test all combinations, however each treatment group (VEH and ketamine 10/30mg/kg) of 12 rats were exposed to the same combinations in duplicate. The stimulus position within area-A/B (Figure 1) was predetermined by a priori pseudorandom sequence.

3. Results

Thirty seven rats successfully completed the attentional set shifting task; seven rats were excluded due to incompletion of the test. The three treatment groups where; VEH + VEH (n=12), VEH + ketamine 10mg/kg (n=14) and VEH + ketamine 30mg/kg (n=11). A 3-way analysis of variance (ANOVA) was used to analysis the number of trials to criterion (between subject factors were defined by treatment group and paradigms). Analysis indicates a significant interaction between discriminations ($F(6,186)=13.4$, $p<0.0001$) and treatment groups ($F(12,186)=3.4$, $P<0.0001$). As there was no significant interaction between trials to completion and paradigms ($F(6,186)= 1.9$, $P=0.084$), subsequent statistical tests was analysed by 2-way ANOVAs. Data was also analysed by; LSD corrected post hoc multiple comparisons to determine significance between treatment groups.

3.1 Habituation acquisition

Rats underwent habituation prior to initiating the set shifting task, consisting of a simple odour and medium discrimination (Figure 5). We first examined the effect of treatment on each discrimination test by a 2-way ANOVA (medium and odour discrimination within subject's factors and treatment group between subject factors). Analysis revealed a significant interaction between treatments group and acquisition of the odour discrimination ($F(2,34)=5.506$, $p=0.008$), in contrast to the medium discrimination which

just missed significance (F(2,34)=2.533, p=0.094). During the odour discrimination ketamine (30mg/kg) treated animals, required significantly more trials to criterion relative to VEH (P=0.004) and ketamine (10mg/kg) (P=0.012). Analysis of the odour discrimination by post hoc analysis identified a significant interaction between the ketamine (30mg/kg) dose with VEH (p=0.004) and ketamine (10mg/kg) (p=0.012). Furthermore, significance was also observed during the medium discrimination between ketamine (30mg/kg) and VEH.

3.1 Discrimination learning

A 2-way ANOVA (discriminations within subject effects and treatment group between subject effects) revealed no interaction within subjects effects between discriminations (F (1,34) = 0.046, p=0.832) and treatment groups (F(2,34)= 0.671, p=0.518). The acquisition of the SD and CD task was achieved with an average of 9 trials (mean (SE) 8.8 (0.51) and 8.9 (6.1), respectfully) to criterion in VEH treated rats. Furthermore, there was no significant difference between treatment groups and discrimination for the SD (F(2,34)=0.220, p=0.804) and CD (F(2,34)=1.611, p=0.215). Although, ketamine (30mg/kg) treated animals on average, required three extra trials to criterions (mean (SE) 10.5(1.7)), relative to VEH (mean (SE) 8.3(0.7)) although this was not significant (p=0.157).

3.2 Reversal Learning

The most important finding from this study was the interaction between ketamine and reversal learning. A 2-way ANOVA (reversal were within subject factors and treatment groups where defined as between subject factors) revealed ketamine produced a significant difference between all three reversals (F(2,68)=3.797, p=0.027). A 1-way ANOVA identified a significant interaction between treatment groups and reversal acquisition (trial to criterion), for REV1 (F(2,34)=10.1 (p<0.0001), REV2 (F(2,34)=7.372 (p=0.002)) and REV3 (F(2,34)=10.1 (p=0.020)).

In addition, Post hoc analysis identified significance between ketamine (30mg/kg) treated animals with ketamine (10mg/kg) and VEH during REV1. Analysis of REV2 revealed a significance difference between VEH and ketamine (10/30mg/kg) treatment. Furthermore, significance was also established between VEH and ketamine (30mg/kg) during REV3. Analysis of the number of trials to criterion (Figure 2), indicates on average REV3 (mean (SE)= 13.1(0.78) required less trials to reach criterion in comparison to REV1 (mean(SE)=17.18(1.03) and REV2 (mean(SE)=16.64(1.71).

A 2-way ANOVA (reversals were identified as within subjects factors and treatment group was identified as a between subject factor) indicated significance within REV1 and REV3 (F(1,10)=6.85, p=0.026), whilst REV2 and REV3 approached significance (F(1,10)=3.58, p=0.088). Similarly, trials to criterion (Figure 2) and errors to criterion (Figure 3) both produced a dose-dependent response between treatment groups. However, no significant difference was observed between ketamine treatment groups and errors to criterion for each reversal (e.g. ketamine (10mg/kg) vs. ketamine (30mg/kg) (p=0.445), although significance was established relative to VEH (e.g. REV1, VEH vs. ketamine (30mg/kg) (p<0.0001)).

A clear trend emerged between ketamine treatment and latency for reversal completion. A 2-way ANOVA (reversal within subject and treatment groups between subjects factors) indicated significance (F(2,68)=4.021, p=0.022) . REV1 and REV2 showed a trend between ketamine treatment and latency, REV1; (mean (SE), 18.16(2.93), 24.16(2.79), 28.07(5.40)) and REV2; (mean (SE), 18.49(4.22), 30.79(6.20), 34.34(6.00)), respectfully (Figure 4). Interestingly, in respect to ketamine treatment (10 and 30mg), REV2 revealed the most significant interaction between latency and errors to criterion; (F(1,36)=5.05, p=0.052) and (F(1,36=13.878 p=0.001), respectfully.

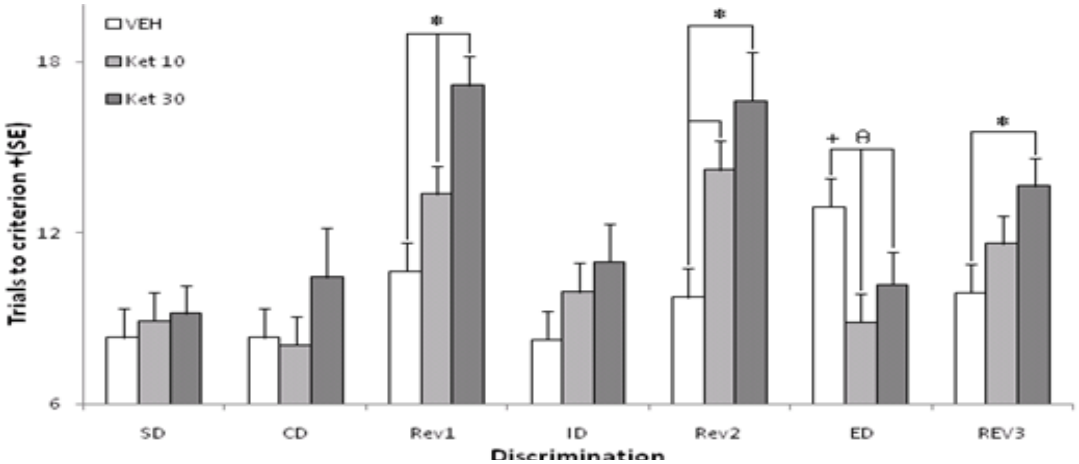

Figure 2: Bar chart shows the number of trial to criterion (six consecutive error free retrieval) in an attention set shifting task in three treatment groups (VEH +VEH; 1ml/kg, ketamine 10mg/kg and VEH + ketamine 30mg/kg). Ketamine treated rats required significantly more trials to reach criterion during REV1, 2 and 3 relative to controls (* p<0.05). Rats treated with ketamine (10mg/kg) required less trials to criterion for REV1, relative to ketamine (30mg/kg) (* p<0.05), although required more trials to reach criterion for REV2, relative to VEH (# p<0.05). ID-ED shift (+p=0.007). VEH treated rats required more trials to criterion during the EDS relative to ketamine (10/30mg/kg) (θ p<0.05). Results reported as mean ± standard error

3.3 ID-ED Shift

The second important finding from this study was the interaction between ketamine and the EDS. A 2-way ANOVA (treatment group was between subject effects and ID/EDS shift was within subject effects) was used to examine the effects of ketamine treatment on the ID and ED shifts. Analysis revealed no interaction within discriminations ($F(1,34)=1.428$, $p=0.240$), although significant was observed between treatment group and discrimination ($F(2,34)=5.85$ $p=0.007$).

A 1-way ANOVA identified a significant difference between treatment groups for EDS ($F(2,34)=5.436$ $p=0.009$), but not IDS ($F(2,34)=1.574$ $p=0.222$). Furthermore, multiple comparisons analysis revealed significance when VEH was compared with ketamine (10mg/kg) ($p=0.003$) and ketamine (30mg/kg) ($p=0.046$).A 1-way ANOVA (treatment groups where between subject effects and ID/EDS shift within subject effects) identified a significant difference between IDS and EDS for VEH treated animals ($F(2,11)=11.2$, $p=0.007$), but not ketamine (10mg/kg) or ketamine (30mg/kg).

In contrast, there was no significant difference between the IDS and EDS tasks for ketamine (10mg/kg) ($F(1,13)=0.647$, $p=0.436$) or ketamine (30mg/kg) treated animals ($F(1,10)=0.439$, $p=0.522$). In addition, VEH treated rats required on average four extra trials to criterion for the EDS task (mean (SE) trials = 12.92(1.03) compared to the ID task (mean (SE) trials = 8.25 (0.79).

This data suggests the ED shift was more complex to interpret than the IDS, since VEH treated animals required more attempts to reach criterion. Attentional sets were formed for VEH treated rats, analysis of the number of trials to criterion ($p=0.007$) and the number of errors to criteria ($p=0.002$) clearly identified a significant difference between the ID-ED shifts. Furthermore, ID-EDS deficit was not observed in ketamine-treated rats, thus questioning the formation of attentional sets prior to the EDS task.

3.4 Latency

A 2-way ANOVA (discriminations within subject and treatment groups between subject factors) identified a significant interaction between discrimination completion time and treatment groups ($F(6,204)=4.513$, $p<0.0001$). Although, ketamine (30mg/kg) just missed statistical significance during REV1 ($p=0.077$) and REV3 ($p=0.065$). The average time to completion was very similar between treatment groups for the SD, CD and REV3.
Although observation of the bar displaying the latency (Figure 4), one can clearly identify ketamine (30mg/kg) treated animals on average required longer than controls during REV1 (mean (SE)= (18.16(2.93)) vs. (28.68(2.39)), ID (mean (SE)= (18.49(4.22)) vs. (29.15(7.24)), REV2 (mean (SE)= (17.38(4.50)) vs. (34.24(6.00)) and ED (mean (SE)= (18.22(3.13)) vs. (26.58(7.11)).

3.5 Statistical Analysis

Analysis of data was achieved through SPSS for windows, version 17. Statistical significance was defined at $p<0.05$.

4. Discussion

The aim of this study was to evaluate the effects of a five day sub-chronic ketamine administration regime on an attentional set-shifting paradigm in male Lister hooded rats, adapted from the model described by Birrell and Brown (41). The study clearly shows sub-chronic ketamine administration mediates a deficiency in reversal learning, whilst, interestingly improving performance of the ED discrimination. In contrast to the simple and compound discriminations where the stimuli are unchanged, reversal learning requires cognitive inhibition of previously rewarded stimuli. Ketamine treated rats were capable of acquiring novel awarded stimuli, as shown by the ID and ED shifts, thus a possible explanation for the impaired reversal decimations, is the perseveration of responses to stimuli which have been previously reinforced by food-rewards.

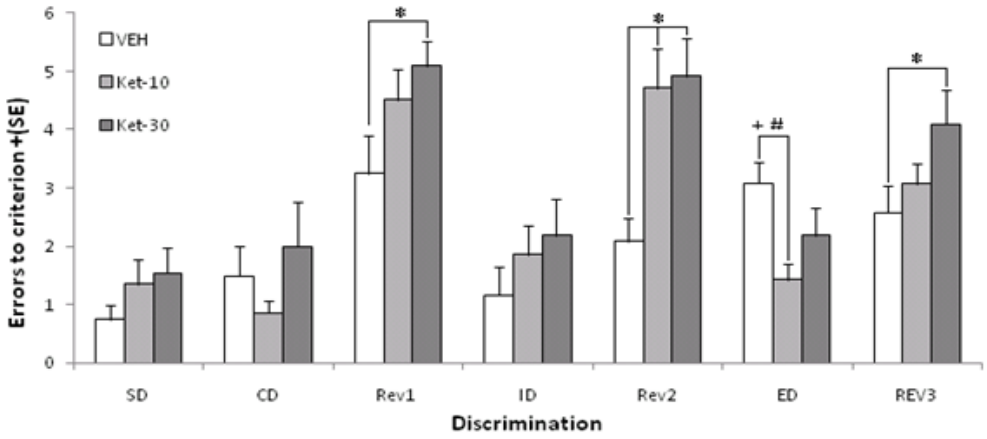

Figure 3: Bar chart shows the number of errors to criterion for each discrimination for each treatment group (VEH +VEH; 1ml/kg, ketamine 10mg/kg and VEH + ketamine 30mg/kg). ketamine (30mg/kg), resulted in an increase in errors to criterion for each reversal (REV1-3), relative to VEH (* $p<0.05$). The 10mg dose of ketamine, increased the number of errors during REV2, relative to VEH (* $p<0.05$). VEH treated rats made more errors to criterion during the EDS, in comparison to ketamine (10mg/kg) (# $p<0.05$). ID-ED shift (+ $p=0.002$) .Results reported as mean ± standard error

4.1 Reversal learning

At first glance our results are somewhat contradictory, in contrast to sub-chronic PCP administration regime, which result in significant EDS impairment (43, 47-49). On closer inspection, PCP studies in which dosing schedules lasted ≤7 days, were associated with a substantial increase in the average number of trials to criterion during certain reversals (42, 47, 48), compared to longer dosing regimens (43, 49). The increased duration of administration and enhanced potency of PCP may result in enhanced neocortical and limbic dysfunction. In addition, sub-chronic PCP administration in mice prior to set-shifting not only attenuated the ID-ED shift but also impaired reversal acquisition(50). Specific operant reversal learning paradigms have also shown impairments in reversal learning following PCP exposure (51). Furthermore, Selective NMDAR antagonist, MK-801 impairs and abolishes reversal learning, at low and high doses, respectfully, in a serial reversal task in a skinner box (52). Psychomotor stimulants (e.g. cocaine) also impair reversal learning (53, 54).

Ketamine has a vast expanse of uses other than simply providing a model for schizophrenia, these include induction of anaesthesia to analgesia for neuropathic pain; therefore it is rather obvious that ketamine and its analogue PCP modulate a range of receptors, in comparison to selective NMDA antagonist, MK-801. The main site of action of ketamine are NMDA receptors on GABA interneurons, however ketamine also modulates a range of other neurotransmitter systems. These include; μ opioid receptor (55), σ non opioid receptor (55), 5HT/DA/NA receptors (56, 57), muscarinic (58) and nicotinic (59) Ach receptors and GABA-A receptors (60). Even though PCP is an analogue of ketamine, their pharmacokinetics are somewhat different. The differences in pharmacokinetics may account for the attenuated response obtained during attentional set shifting. For example, PCP has a high affinity for the D2 receptor whilst having a low affinity to the NMDAR. In contrast, ketamine has a high affinity for the D2 receptor but a higher affinity for the NMDAR (61).

In addition, it has been elucidated that unoccupied non-NMDA, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) and kainate receptor may also play a role in the neurobiological events following NMDAR antagonist administration (20). In contrast to the medial prefrontal cortex (mPFC) which is important for EDS acquisition, the OFC has been identified as a significant regulatory site for reversal learning. Reversal deficits following OFC attenuation (e.g. lesioning) have been reported in numerous studies which vary in stimulus form, these include; olfactory (46, 62, 63), tactile (46) and visual cues (64, 65).

McAlonan and Brown lesioned the OFC prior to set shifting, this resulted in reversal deficits similar to that observed in our study (46). However, there are some distinct differences. OFC lesioning resulted in significant comparable deficits during all three reversals (REV1-3), whilst our studies clearly shows a dose response impairment in reversal learning, with only the ketamine (30mg/kg) reporting significance for each reversal. However, OFC lesions may possibly result in greater functional changes in comparison to the pathology mediated by ketamine. Furthermore, repeated exposure to reversal discriminations (REV1-3) has resulted in a significant improvement in the number trials to criterion, when REV1 is compared with REV3 for ketamine (30mg/kg) treated animals (p=0.026). On the contrary, OFC lesioned rats did not show improved acquisition of reversal learning following subsequent exposure (46). In addition; OFC dependent reversals deficits can be attenuated by basolateral amygdala lesions (66). NMDAR hypofunction of the cortical pyramidal neurones can attenuate neuronal communication between brain regions, thus, causing the hyperactivation of pathways (e.g. between OFC and mPFC),

4.2 Improved ID-EDS performance or inability to form attentional sets?

The ketamine profile observed in this study does not show EDS deficits, similar to those induced by PCP (47, 49, 67). Nevertheless, the ID-ED shift was significant for VEH treated rats (p=0.007). Thus indicating, VEH treated rats formed an attentional set prior to the ED shift.

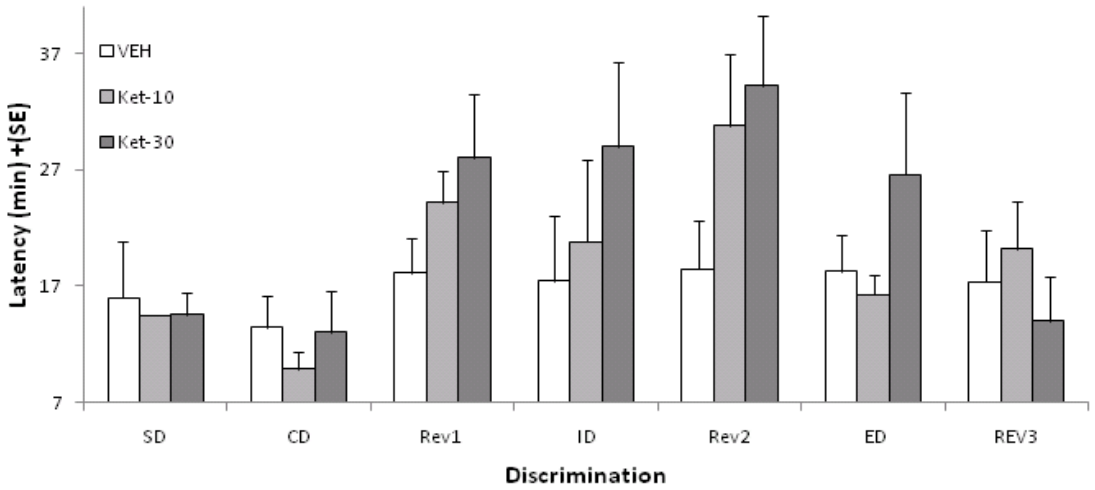

Figure 4: Bar chart shows the latency for each discrimination and treatment group (VEH +VEH; 1ml/kg, ketamine 10mg/kg and VEH + ketamine 30mg/kg)**.** Results reported as mean ± standard error.

Our results have been slightly complicated by the fact; ketamine (30mg/kg) treatment resulted in a deficiency in the acquisition of the odour and medium habituation discriminations. Unlike other attentional set shifting studies where the animals where extensively habituated prior to testing, our habituation criteria was simply the completion of two simple discriminations which incorporated two dimensions. Therefore, it could be argued that ketamine induced a lasting neurological change resulting in a deficiency in the ability to form attentional sets. In addition, ketamine induced cognitive deficits during habituation could possibly be normalised relative to VEH with extensive habituation, thus enabling ketamine treated rats to form an attentional set.

The classic set-shifting paper by Birrell and Brown has clearly reported lesioning of the mPFC results in deficits in the formation of attentional sets (41). Subsequently; if the former is correct and ketamine had mediated chronic neurological adaption, it can be suggested ketamine has improved the performance mPFC. 6-hydroxydopamine lesions of the PFC in marmoset monkeys, improved ED shift performance, however this was thought to be due to the inability to establish attentional sets (68). McAlonan and Brown; reported OFC lesions resulted in impaired reversal acquisition whilst improving EDS performance, thus questioning the formation of attentional sets (46). A subsequent study by Brown and colleagues has shown mPFC lesions can be attenuated by asenapine, as asenapine enhances neuronal activity in the anterior mPFC (69). In contrast to lesioning, assessing pharmacological modulation studies have also been exploited, in an event to ascertain pre-frontal involvement during set-shifting (16, 70).

4.3 Set shifting in primates

Ketamine administration in primates prior to an task switching paradigm slows performance and attenuates task switching accuracy (11). Selective PFC 5-HT depletion in marmoset monkeys mediates a perseverative impairment in OFC dependant reversal learning (71). Moreover, selective 5HT OFC depletion impaired performance in a SDR task, whilst selective OFC dopamine depletion did not induce deficits in reversal learning. This impairment was thought to be due to the perseveration of previously rewarded stimuli (72). It is well understood that lesioning the OFC impairs cognitive flexibility; however OFC lesioned rhesus monkeys did not show impairments relative to controls during the reversed reward contingency task (73). However, Man et al. repeated the reversed reward contingency task but lesioned the OFC or medial striatum in marmosets, this resulted in attenuated acquisition and impaired reversal learning due to preservation of the previously rewarded stimuli (74). Dias et al. investigated OFC lesioning in marmoset monkeys during a set-shifting paradigm, interestingly they only observed reversal deficits during the first reversal (45). Reversal attenuation has also been observed in rhesus monkeys following OFC lesioning (75). This suggests, primates have enhanced cortical flexibility to enable them to acquire and apply past experience as they progress though the task, in contrast to rodents which show perseveration of previously relevant stimuli (46). Ketamine may induce functional abnormities within the OFC, but the deficiencies are subsequently improved following repeated exposure, possibly due to the involvement of other neuronal pathways.

4.4 Reversal learning deficits in schizophrenic patients?

The Cambridge Neuropsychological Test Automated Battery (CANTAB) is a range of computerized tests to assess memory, attention and executive function in humans. CANTAB has been evaluated and standardised to assess a range of pathologies, including schizophrenia (76). Attentional set-shifting assessment in schizophrenic patients has clearly identified ID-EDS deficits (77-79). In addition, some studies have also identified significant impairments in reversal learning (77, 79). Tyson et al. reported, clinical set-shifting ability remained unchanged over a nine month period following ID-EDS assessment though CANTAB (80) (other studies using similar measures have paralleled these findings (81, 82)). Turner et al. administered modafinil to schizophrenic patients prior to an ID-EDS task, this resulted in significantly more patients completing the ED shift in comparison to placebo, thus suggesting EDS performance can be improved in vivo(78).

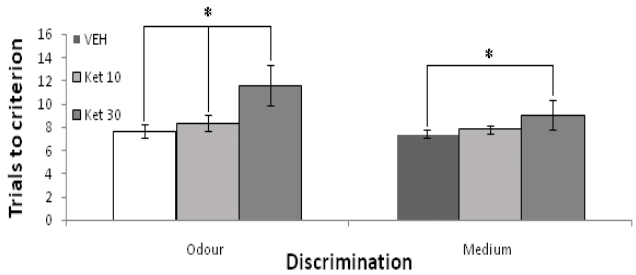

Figure 5: Bar chart shows the number of trial to criterion (six consecutive error free retrievals) for each treatment group (VEH +VEH; 1ml/kg, ketamine 10mg/kg and VEH + ketamine 30mg/kg) during the odour and medium habituation task. The 30mg dose resulted in more trials to criterion in comparison to VEH or ketamine (10mg/kg), during the odour discrimination. Ketamine (30mg/kg), required more trials to reach criterion during the medium discrimination, relative to VEH (* $p<0.05$).

5. Summary

The aim of this study was to help characterise the cognitive impairments induced by a five day sub-chronic ketamine regime in an attentional set-shifting paradigm. We have clearly identified the ability of ketamine to disrupt reversal learning. Reversal learning deficits have also been identified in schizophrenic patients though the CANTAB battery of tests. This suggests a possible role for examining ketamine-induced cognitive deficits in rats, which could be utilized to assess the efficacy of novel cognitive enhancing compounds.

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