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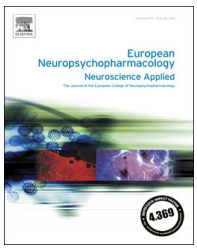

Partial agonism at the α7 nicotinic acetylcholine receptor improves attention, impulsive action and vigilance in low attentive rats

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5C-CPT;
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Abstract
Inattention is a disabling symptom in conditions such as schizophrenia and attention deficit/hyperactivity disorder. Nicotine can improve attention and vigilance, but is unsuitable for clinical use due to abuse liability. Genetic knockout of the α7 nicotinic acetylcholine receptor (nAChR) induces attention deficits therefore selective agonism may improve attention, without the abuse liability associated with nicotine. The α7 nAChR partial agonist encenicline (formerly EVP-6124) enhances memory in rodents and humans. Here we investigate, for the first time, efficacy of encenicline to improve attention and vigilance in animals behaviourally grouped for low attentive traits in the 5 choice-continuous performance task (5C-CPT). Female Lister Hooded rats were trained to perform the 5C-CPT with a variable stimulus duration (SD). Animals were then grouped based on performance into upper and lower quartiles of d′ (vigilance) and accuracy (selective attention), producing high-attentive (HA) and low-attentive (LA) groups. LA animals showed an increase in selective attention and vigilance at 0.3 mg/kg encenicline, a reduction in impulsive action (probability of false alarms) and increase in vigilance following 1 mg/kg at 0.75 s SD. At 1 mg/kg, HA animals had *reduced* selective attention at 0.75 s SD and *reduced* vigilance at 0.75 and 1.25 s SD. Improvement of attention, vigilance and impulsive action in LA animals demonstrates that encenicline has pro-attentive properties dependent on baseline levels of performance. Our work suggests that α7 nAChR partial agonism may improve attention particularly in conditions with low attention.

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1. Introduction

Attention can be broadly defined as the ability to filter out irrelevant stimuli in order to optimise limited neurochemical resources (Luck and Gold, 2008). Inattention is an early symptom in highly disabling conditions such as schizophrenia, bipolar disorder, Alzheimer's disease and attention deficit/hyperactivity disorder (ADHD) (Luck and Gold, 2008; Foldi et al., 2002).

Nicotine acts at nicotinic acetylcholine receptors (nACh) to produce pro-cognitive effects, in particular enhanced selective attention. This effect has been demonstrated in non-smoking adults using the continuous performance task (CPT) (Rezvani and Levin, 2001), in rodents using the 5 choice continuous performance task (5C-CPT) (Young et al., 2013) and in the 5 choice serial reaction time task (5C-SRTT) (Grottick and Higgins, 2000). In healthy non-smokers, nicotine improves attention most in low performing individuals (Wignall and DE Wit, 2011; Poltavski and Petros, 2006). In animals, this has been demonstrated using the 5C-SRTT where nicotine produces a greater improvement in low performing animals (Grottick and Higgins, 2000).

Smoking in schizophrenia patients may be a form of self-medication (Segarra et al., 2011; Parikh et al., 2016; Young and Geyer, 2013). This idea is supported by the higher prevalence of smoking in schizophrenia patients (86–90%) compared to healthy controls (15–25%) and improvement of cognitive domains, including vigilance and attention, in schizophrenia patients and healthy subjects following nicotine treatment in the CPT (Rezvani and Levin, 2001; Heishman et al., 2010; Segarra et al., 2011). However, nicotine has a high abuse liability and many unpleasant side effects including dizziness, headache, agitation, anxiety and loss of appetite (White and Levin, 1999; Watkins et al., 2000). This makes it unsuitable as a treatment, particularly for schizophrenia and ADHD patients who often also exhibit high levels of impulsivity, which further increases the risk of drug addiction.

The $\alpha4\beta2$ and $\alpha7$ receptors are the most abundant nicotinic acetylcholine receptor (nAChR) subtypes in the CNS. The $\alpha7$ nAChR is a pentameric ligand gated ion channel located both pre and post synaptically throughout the cortex enabling fast synaptic neurotransmission (Vizi and Lendvai, 1999). Mice with a deletion of the $\alpha7$ nAChR show cognitive deficits including reduced sustained attention, supporting a role for $\alpha7$ nAChR mechanisms in attention (Young et al., 2007; Hoyle et al., 2006). It has also been shown that attention deficits in $\alpha7$ receptor knockout mice can be reversed by $\beta2$ receptor agonists (Kolisnyk et al., 2015). This suggests that activation of $\beta2$ nAChRs can also restore attentional deficits due to $\alpha7$nAChR deficiency. However, the $\beta2$-containing heterodimeric (largely $\alpha4\beta2$) nAChRs are predominantly implicated in nicotine dependence via activation of the mesolimbic dopamine system (Picciotto et al., 1998; Bloem et al., 2014; Brioni et al., 1996; Pons et al., 2008). Therefore $\alpha7$ receptor activation represents a more favourable target.

We have shown previously that in sub-chronic phencyclidine (PCP) treated rats (a well validated model for schizophrenia, Mclean et al., 2011) and in healthy control animals (Mclean et al., 2016; Mclean et al., 2011) the $\alpha7$ full agonist PNU-282987 improves performance in novel object recognition, a visual recognition memory task. In contrast, the same compound has been shown *not* to improve attention or vigilance in the 5C-CPT in both normal mice and in those with a scopolamine-induced deficit (Young et al., 2013). This lack of efficacy is in agreement with other studies using $\alpha7$ full agonists in tasks of attention, suggesting that visual recognition memory, not attention is improved by full agonists of the $\alpha7$ receptor (Young and Geyer, 2013).

However, the $\alpha7$ partial agonist ABT-126 produced a significant increase in attention in a phase II clinical study when assessed using the MATRICS Consensus Cognitive Battery (Haig et al., 2016), and this is supported by the effects of tropisetron and R-3487, which are also $\alpha7$ receptor partial agonists. Both compounds are also antagonists at the 5-HT_3 receptor, but antagonism at the 5-HT_3 receptor does not improve attention (Muir et al., 1995). Tropisetron improved sustained attention in schizophrenia patients assessed with the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Shiina et al., 2010) and R3487 improved sustained attention in a visual signal detection task in rodents, these results await clinical confirmation (Rezvani et al., 2009). Partial agonists at the $\alpha7$ receptor have not been studied in animals using a specific task of attention such as the 5C-CPT, nor have their effects been investigated in low attentive animals.

Encenicline is a potent and selective $\alpha7$ nAChR partial agonist and 5-HT_{3A} receptor antagonist (Prickaerts et al., 2012). However, at low nanomolar concentrations in the brain, it is thought that 5-HT_3 receptor binding is minimal, but could reduce side-effects such as nausea via peripheral action (Prickaerts et al., 2012). In rats, a dose of 0.3 mg/kg of encenicline improves visual recognition memory in the novel object recognition task with a 24 hour inter-trial interval in normal rats and reverses a scopolamine-induced deficit in the same task (Prickaerts et al., 2012).

The 5C-CPT is a test of sustained/selective attention, impulsive action and vigilance, developed from the clinically used CPT. It is also based on the widely-used rodent 5C-SRTT. However, it provides enhanced validity and translation to the clinic compared with the 5C-SRTT by including trials where no response is required. Comparing the two, the 5C-CPT is the more translational, whereas the 5C-SRTT offers higher throughput (Lustig et al., 2013). In both of these tasks, several studies have separated animals into groups based on variation in their task performance, which are stable across multiple test sessions (Blondeau and Dellu-Hagedorn, 2007; Dalley et al., 2007; Grottick and Higgins, 2000; Tomlinson et al., 2014); reviewed in Hayward et al. (2016)). We have demonstrated that animals respond differentially to pharmacological treatments, in particular methylphenidate and atomoxetine, drugs currently used to treat ADHD in patients, based on this natural variation of performance when the test parameters of the 5C-CPT are manipulated (Tomlinson et al., 2014; Tomlinson et al., 2015). It is our view that this

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paradigm offers an unbiased method to study attentional deficits of relevance to several disorders without assuming a mechanism, as is the case with genetic or chemical manipulations (Hayward et al., 2016).

Effects of a partial agonist at the α7 nAChR on attention and vigilance have yet to be studied using the 5C-CPT and, as nicotine has a greater effect to improve attention in low performing groups, our aim was to compare the effects of encenicline in high and low attentive rats. We hypothesised that encenicline would improve attention in the 5C-CPT, particularly in low-attentive animals.

2. Experimental procedures

2.1. Animals

37 female Lister Hooded rats (Charles River, UK; weighing 210 ± 20 g at the start of training) were housed in groups of four or five in individually ventilated cages with two levels (GR1800 Double-Decker Cage, Techniplast, UK) under a standard 12 hour light: dark cycle (lights on 7:00 am). We used female rats as the 5C-CPT has been carefully validated in female rats in our laboratory (Tomlinson et al., 2014; Tomlinson et al., 2015; Barnes et al., 2012a, 2012b). In addition, male rats grow rapidly, which precludes social housing over the lengthy period of time it takes to train and test rats in the 5C-CPT. Individual housing is stressful for this social species and best avoided (Holson et al., 1991; Brown and Grunberg, 1995). The environment was maintained at 21 ± 2 °C, 55 ± 5% humidity. The diet was standard rat chow (Special Diet Services, UK) controlled to maintain 90% free feeding weight throughout training and testing (typically 10 g/rat/day). Water was available *ad libitum* for the duration of the study, except in the operant chambers. All experiments were conducted between 09:00 and 17:00 in the light phase. All experiments were conducted in accordance with the UK Animals (Scientific Procedures) 1986 Act and local University ethical guidelines.

2.2. Apparatus

Tests were conducted in eight standard nine-hole chambers (Campden Instruments Ltd, UK) with holes 2, 4, 6, and 8 occluded. Chambers and data collection were controlled by ABet II Touch software (Lafayette Instrument Company, IL, USA). Animals' behaviour was reinforced with 45 mg rodent reward pellets (Test Diet, MO, USA).

2.3. 5C-CPT training procedure

Animals were trained as described previously (Barnes et al., 2012a, 2012b; Tomlinson et al. 2014). In brief, animals respond to one of five holes when they detect a light stimulus. A nose poke either while the stimulus is on (stimulus duration (SD)) or within a set period after it first coming on (limited hold) causes release of a food reward. Rare no go trials are also interspersed (30% of trials), in these all 5 lights illuminate and no response is required to get a food reward. Incorrect responses, missed go trials and responded to no go trials are punished with a 5 s time out with the house light on. When food is dispensed or at the end of the time out, the food tray lights up and nose poke for collection of the food reward starts a timer before the next trial (inter-trial interval (ITI)). A response during this period is considered a premature response and also results in a time out period. Animals were trained for approximately 24 weeks to set a set criteria and final training parameters of 2 s SD, 2 s limited hold, 5 s ITI. This was conducted in a series of stages with successively longer SD and limited hold where each stage was reached by meeting criteria of >70% accuracy, <25% omissions and >65% correct rejections (see Barnes et al. (2012a) and Barnes et al. (2012b). Once rats reached these final criteria, they were trained once per week in order to maintain performance and avoid over-training.

2.4. Testing procedure

Testing parameters were as per final training criteria, with a variable 0.75, 1.25 and 2s SD and increased 7-12s variable ITI. As a previous study found separable genetic effects of α7 receptor mutations at different SDs, a variable SD was used here (Young et al., 2013; Young et al., 2007). In order to gather sufficient data for three SDs, the session was extended to 1 h or 250 trials, whichever came first.

Encenicline ((R)-7-chloro-N-(quinuclidin-3-yl)benzo[b]thiophene-2-carboxamide; kindly donated by Autifony Therapeutics, Verona, Italy), was prepared at concentrations of 0.1, 0.3 and 1 mg/kg in distilled water and administered by oral gavage 30 min before testing in a volume of 2 ml/kg. Each test day was separated by a seven day washout period (no drug administration, or training in 5C-CPT). Treatments were randomly assigned based on a within-subjects latin square design. Doses were selected from published studies showing efficacy in novel object recognition in rats (Prickaerts et al., 2012; Van Goethem et al., 2015).

2.5. Division into subgroups

Animals were divided into high and low performing groups based on performance when treated with vehicle (0.9% saline). The best performing 10 animals for d′ and accuracy formed the high-attentive (HA) group and the worst performing 10 animals formed the low-attentive (LA) group. This is an upper/lower quartile split, which represents a careful balance between having significantly different groups and the number of animals used (see Hayward et al. (2016)). To achieve this, animals were ordered by d′ and the highest/ lowest 10 animals were chosen, providing their accuracy was also above/below average. As vigilance is a measure of overall performance across go and no go trials, accuracy was also used to separate the group into an attention phenotype. Two animals were excluded for making >80% omissions.

2.6. Statistical analysis

The method for calculation of all parameters is described in detail in Tomlinson et al. (2014) and Young et al. (2013). The signal detection theory measure d′ was used in this case only after confirming that probability hit rate (pHR) and probability of false alarms (pFA) were normally distributed, as described in Young et al. (2013). Here, d′ is calculated in the same way as described in Young et al. (2013) as the z score of pHR minus the z score of pFA.

$$pHR = \frac{CorrectResponse}{CorrectResponse + IncorrectResponse + MissedTrials}$$

$$pFA = \frac{FalseAlarm}{FalseAlarm + CorrectRejection}$$

$$d' = z(pHR) - z(pFA)$$

$$RI = \frac{pHR + pFA - 1}{1 - (pFA - pHR)^2}$$

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Using d′ is a further translational step towards making the rodent 5C-CPT closer to the human CPT, compared to using sensitivity index (Young et al., 2013). Measures were calculated individually for each rat at each SD for accuracy, omissions, pHR, pFA, d′ and responsivity index (RI) where z scores were based on whole cohort data. After relevant measures were calculated, data were analysed using InVivo Stat (Version 3.4), as the most appropriate statistical package for in vivo behavioural experiments (Clark et al., 2012). Overall performance (Table 1) was compared using a one-way Analysis of Variance (ANOVA) comparing treatment as a factor and using animal ID as a blocking factor to account for the within-subjects design. Between-group comparisons used least square difference (LSD) tests adjusted for multiple comparisons by a Benjamini-Hochberg's procedure. Measures compared by this method include accuracy, pFA and d′ for three SDs. Grouped analysis used a two-way repeated measures mixed model ANOVA with GROUP as the treatment factor and TREATMENT as the repeated factor for each measurement followed by LSD planned comparisons for each treatment compared to vehicle. Normality and Sphericity of the data were judged using the normality plot and the residual vs. predicted plots. Arcsine, square root or Log_{10} transformations were used when appropriate. Data are presented as F values and p values for TREATMENT*GROUP interactions and effects are considered statistically significant if the p value from Fisher protected least square difference planned comparisons were <0.05.

3. Results

3.1. Group performance

It's important to establish overall group performance before separating the animals into the groups, particularly when within group reference points are used (Hayward et al., 2016), using parameters such as upper/lower quartiles (Table 1). Comparison for all ($n=37$) animals showed no significant difference between treatment levels following a one way ANOVA with animal ID as a blocking factor.

3.2. High/low comparison

Comparison of the main measures (Accuracy, pFA and d′; Figure 1) using adjusted LSD tests found that HA and LA

Table 1 When considered as a single cohort no treatment effect of encenicline was observed.

Measure	Variant	Vehicle	0.1 mg/kg	0.3 mg/kg	1.0 mg/kg
Accuracy	0.75 s	93±1.5	90±1.6	93±1.5	90±1.5
	1.25 s	95±1.2	97±0.62	97±0.57	96±0.95
	2 s	96±0.90	97±0.91	98±0.53	97±0.94
Omissions	0.75 s	44±2.8	47±2.6	43±2.6	48±2.6
	1.25 s	38±2.9	40±3.0	37±2.8	41±2.8
	2 s	36±3.1	38±2.9	33±3.2	36±2.5
pFA	0.75 s	0.23±0.028	0.20 ±0.024	0.21±0.027	0.19±0.024
	1.25 s	0.24±0.026	0.22±0.019	0.26±0.027	0.22±0.027
	2 s	0.23±0.020	0.21±0.02	0.23±0.023	0.24±0.023
d′	0.75 s	0.029±0.22	-0.11±0.23	0.059±0.23	-0.053±0.21
	1.25 s	0.065±0.22	-0.092±0.18	-0.033±0.21	-0.077±0.25
	2 s	-0.086±0.22	0.14±0.23	0.094±0.20	-0.32±0.20
RI	0.75 s	0.32±0.055	0.21±0.056	0.26±0.052	0.18±0.053
	1.25 s	0.35±0.048	0.26±0.050	0.38±0.045	0.29±0.043
	2 s	0.36±0.046	0.33±0.047	0.39±0.044	0.33±0.048
Trials	0-20 min	69±0.98	68±1.1	70±0.98	66±2.0
	21-40 min	68±1.1	69±1.5	69±1.1	67±1.1
	41-60 min	56±2.0	54±2.0	56±2.2	56±2.0
Premature	-	11±1.4	7.4±1.1	11±2.1	11±1.7
Correct latency	-	0.82±0.022	0.85±0.023	0.82±0.023	0.83±0.022
Incorrect latency	-	0.95±0.069	1.2±0.054	1.0±0.054	1.0±0.065
Magazine latency (Go)	-	1.1±0.024	1.1±0.038	1.0±0.029	1.0±0.028
False alarm latency	-	0.74 ±0.031	0.75±0.031	0.73±0.032	0.71±0.030
Magazine latency (No Go)	-	10±1.5	9.8±1.4	11±1.5	13.±1.8

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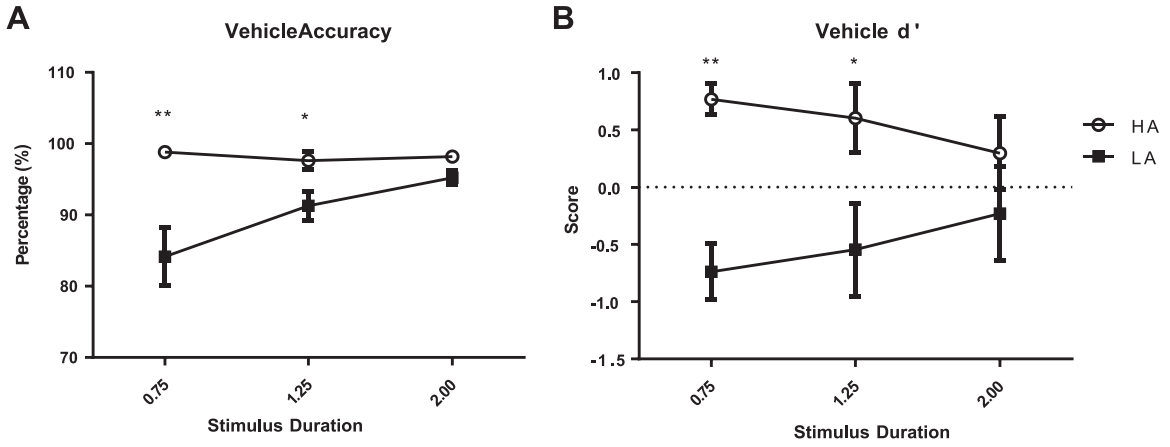

Figure 1 Group differences between high and low attentive groups (HA/LA) at increasing SDs. During saline treatment the difference between HA/LA is most significant at the most challenging (i.e., shortest) stimulus duration (0.75 s), with LA showing significantly lower attention (Accuracy; A) and d′ (vigilance; B). Data are shown as mean ± SEM. $n=10$ HA and $n=10$ LA animals. *, **, denote significance levels $p<0.05$, 0.01 of Benjamini-Hochberg's procedure adjusted LSD planned comparisons comparing HA with LA groups at each SD.

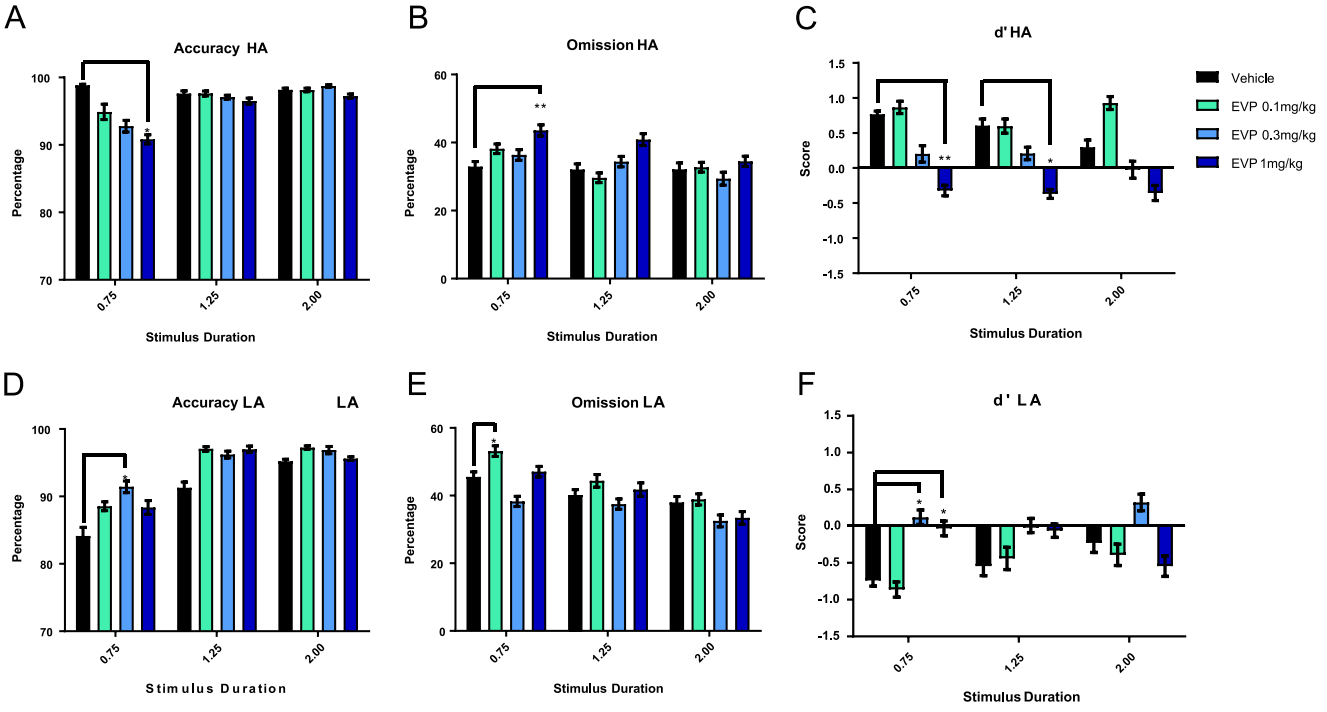

Figure 2 Encenicline improved selective attention and vigilance in low attentive (LA) animals only. In HA animals, 1 mg/kg encenicline significantly reduced performance in accuracy (A), omissions (B) and d′ (D) at 0.75 s SD, d′ was also reduced by the same dose at 1.25 s SD. In LA animals, accuracy (selective attention; D) was significantly increased at 0.3 mg/kg for 0.75, d′ (F) is significantly increased at 0.3 and 1 mg/kg of encenicline at 0.75 s SD and omissions (E) are increased at 0.1 mg/kg at 0.75 s SD. Data are shown as mean ± SEM of $n=10$ HA and $n=10$ LA animals each tested at all doses. * and ** denote significance levels $p<0.05$, 0.01 respectively for LSD planned comparisons of vehicle treated animals to the three treatment levels following significance in GROUP*TREATMENT interaction in a repeated measures two way ANOVA.

groups differed significantly in accuracy and d′ at 0.75 (both $p<0.01$) and 1.25 s (both $p<0.05$) SD. The data show most robust separation at the most challenging (shortest) SD (0.75 s).

In HA animals encenicline impaired performance in a dose-dependent manner as demonstrated by significantly reduced accuracy at 0.75 SD ($F_{3,54}=3.91$, $p=0.013$) an effect that was significant at 1 mg/kg ($p<0.05$) of

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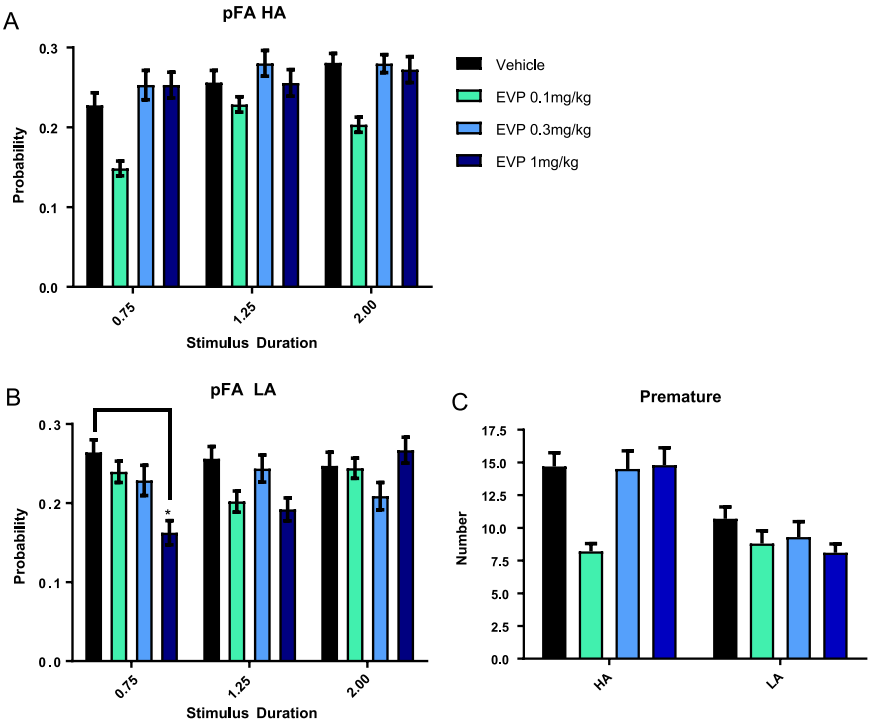

Figure 3 Encenecline reduces impulsivity in LA animals at 0.75 s SD. In HA animals pFA (A) trended to significance for 0.75 s SD and 0.1 mg/kg (p=0.081). Probability of false alarms (pFA; B) significantly reduced in low attentive animals (LA) at 1 mg/kg encenicline at 0.75 SD. No significant effects were seen on premature responses. Data are shown as mean ± SEM of n=10 HA and n=10 LA animals each tested at all doses. *,denotes significance levels $p<0.05$ for LSD planned comparisons of vehicle treated animals to the three treatment levels following significance in GROUP*TREATMENT interaction in a repeated measures two way ANOVA.

encenicline compared with the vehicle treated group, Figure 2. A significant increase in omissions was also observed at 0.75 s SD (Figure 2; $F_{3,\ 54}=2.99$, $p=0.039$) again significant at 1 mg/kg of encenicline ($p<0.01$). These two factors led to a reduction of the signal detection theory parameter d′ (d prime) at all SDs: 0.75 ($F_{3,\ 54}=9.34$, $p<0.0001$), 1.25 s ($F_{3,\ 54}=3.24$, $p=0.029$) 2 s ($F_{3,54}=3.11$,$p=0.034$). Planned comparisons showed significantly reduced d' for 0.75 and 1.25 s SDs at the 1 mg/kg dose ($p<0.01$ and $p<0.05$ respectively, Figure 2). As d′ is a robust measure of vigilance, this suggests that the HA animals became less vigilant as well as less attentive when treated acutely with 1 mg/kg of encenicline. These effects, combined with increased omissions and a lack of significant changes in any of the latency measures and total trials completed suggests that partial agonism of α7 nicotinic receptors induces a reduction in the ability to sustain attention throughout the task in HA animals.

In contrast, encenicline enhanced performance in LA animals as shown by a significant *increase* in accuracy at 0.75 s SD ($F_{3,54}=3.1$, $p=0.034$), an effect that was significant at 0.3 mg/kg of encenicline ($p<0.05$, Figure 2). This change corresponds to an *increase* in selective attention (Robbins, 2002). LA animals also showed increased omissions at 0.75 s SD ($F_{3,\ 54}=2.99$, $p=0.039$). This effect was significant following treatment with the lowest dose of 0.1 mg/kg of encenicline ($p<0.05$), this dose did not produce any other significant effects on attentive measures in either HA or LA animals. Similar to accuracy, d′ showed the opposite effect in LA compared with HA animals and was *increased* (i.e., vigilance was enhanced) at 0.75 s SD ($F_{3,\ 54}=9.34$, $p<0.0001$) with a significant effect produced at 0.3 and 1 mg/kg of encenicline ($p<0.05$, Figure 2).

The impulsivity measure, pFA, was significantly reduced in LA animals at 0.75 s SD ($F_{3,\ 54}=3.1$, $p=0.034$) following treatment with 1 mg/kg encenicline ($p<0.05$, Figure 3) compared to the saline control group. As false alarms represent an impulsive behaviour, this shows reduced response disinhibition, i.e., enhanced inhibitory control (for impulsive action).

No significant effect was seen on the number of trials completed or on any of the latency measures for GROUP*-TREATMENT interaction. This is most likely due to high within-subject variability in these measures as when comparisons between subjects were made (LSD) they were significant for 'no go' magazine latency and incorrect latency. However, the design of this study uses Fisher protection to reduce false positives, so these are not considered valid differences.

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4. Discussion

In order to study the effect of encenicline in high and low attentive animals we firstly established that, after grouping, the animals were significantly different in the measures for attention and vigilance. Treatment with encenicline showed opposite effects between HA and LA groups for accuracy, the correlate of selective attention, where LA animals had enhanced selective attention and HA animals had reduced selective attention. A similar effect was observed for vigilance via the measure d′. For both of these measures 0.3 mg/kg was the optimal dose, i.e., was most effective at the most challenging SD of 0.75 s. An effect was also observed on pFA, but not on premature responses (both measures of impulsive action), these have previously been shown to be separable constructs pharmacologically and genetically (Young et al., 2011). Therefore, our present study shows that LA animals are more able to withhold from responding to a prepotent stimulus but are not significantly different in their ability to wait for the stimulus when treated with encenicline. When assessing false alarms, it is important to evaluate whether reduced responses in 'no go' trials are also seen in 'go' trials, reflecting reduced motivation rather than enhanced response inhibition. Changes in omissions and pFA occurred at different concentrations of the drug suggesting that these effects are independent of one another. The changes we observed in omissions were apparent only for the challenging 0.75 s SD and were observed at 1 mg/kg in HA animals and at 0.1 mg/

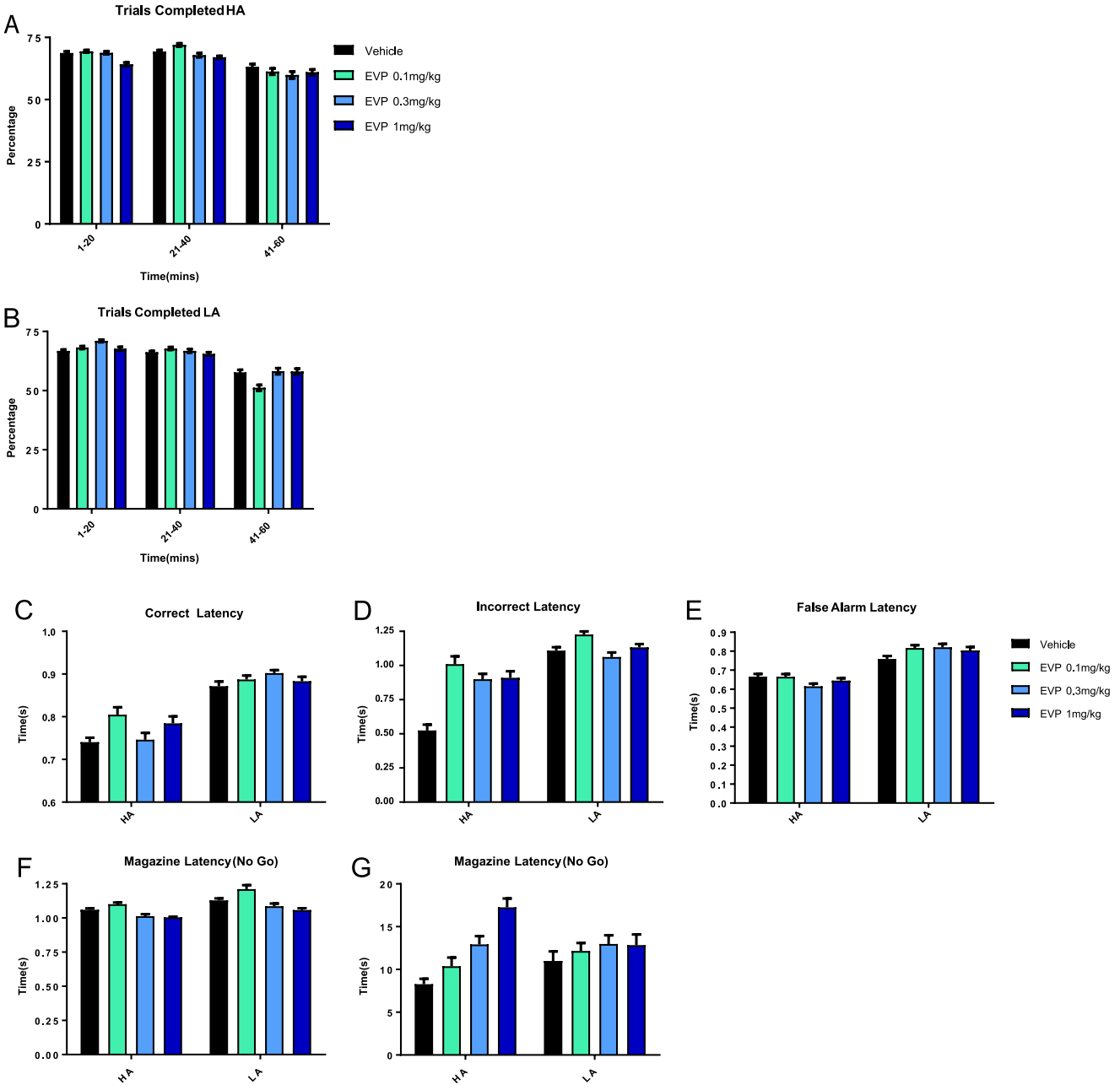

Figure 4 Latency measures of the 5C-CPT showed no significant TREATMENT*GROUP interaction. Data are shown as mean ± SEM of $n=10$ HA and $n=10$ LA animals each tested at all doses.

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kg in LA animals. Changes in omissions can reflect sustained attention, motivation, sedative or motor effects; in order to ascertain which of these are affected other measures are required (Robbins, 2002). Sedative and motor effects should be detected as changes across the latencies; motivational changes would alter the magazine latencies. Incorrect latency and no go magazine latency were significantly different in planned comparisons, but not via the GROUP*-TREATMENT interaction (Figure 3). This is most likely due to high within-subject variability, which is only accounted for in the repeated measures ANOVA. This high variability would require larger group sizes in order to determine whether an effect is robust. However, sedative or motor effects would also be expected to alter correct latency and motivational effects would be expected to alter 'go' magazine latency. As neither of these was observed, the changes in motivation may represent lapses in the ability to sustain attention; however, this requires further testing. The difference in dose required to elicit the effect in HA and LA animals may represent differences in neurobiology between the groups, in agreement with opposing effects seen on other measures. In summary, encenicline improves selective attention and vigilance in LA animals at 0.3 mg/kg and reduces impulsivity at 1 mg/kg.

As we had extended the number of trials to 250 rather than the standard 120 trials, satiety/ reduced motivation are important factors for consideration. Looking at Table 1 and Figure 4A and B the number of trials completed is lower at the final time point, however this was not different between treatment groups suggesting that it did not contribute significantly to the drug effect. This conclusion is further supported by our observation of no significant effect between treatments on magazine latency, a measure of satiety. Using a variable SD enabled us to sample a span of difficulty levels, however, in the 2 s SD, both groups showed $>$90% accuracy suggesting that a ceiling effect may play a role at this SD preventing increases from being detected.

The 5-HT_3 receptor is a homologue of the α7 receptor and so α7 agonists often show appreciable affinity and act as antagonists at this receptor subtype (Prickaerts et al., 2012). However, the selective 5-HT_3 receptor antagonist ondansetron does not improve attention in rats in the 5C-SRTT, suggesting that attention promoting effects seen here are not due to an interaction with the 5-HT_3 receptor (Muir et al., 1995).

Increased accuracy at 0.75 s stimulus duration in LA animals is interesting as it seems to follow an inverted U shaped dose response trend which has been reported for other nicotinic compounds (Kolisnyk et al., 2015; Olincy and Freedman, 2012; Picciotto, 2003). A recent microdialysis study by Huang et al. (2014) found that the effect of encenicline on neurotransmitter efflux in the medial prefrontal cortex differs depending on dose. In that study, 0.1 mg/kg of encenicline increased dopamine, acetylcholine and glutamate release in the prefrontal cortex, whereas only acetylcholine was increased at the higher dose of 0.3 mg/kg. This may be due to receptor populations existing both pre- and post-synaptically, giving the α7 receptor a modulatory role which differs depending on the concentration of acetylcholine at the synapse (Vizi and Lendvai, 1999). An inverted U shaped trend (Yerkes-Dodson effect) is also aproperty of the arousal of attention (Wood et al., 2014) which has been linked to prefrontal monoamine levels (Arnsten, 2009). The theory of optimal arousal and neurotransmitter differences may contribute to the outcomes of this study and would make it interesting to see a combined microdialysis or fast scan voltammetry and attentive task study using encenicline, particularly comparing high/low performing animals.

A previous study found no effect of the α7 full agonist, PNU-282987 in the 5C-CPT in either untreated mice or in those with a scopolamine induced attention/ vigilance deficit, in agreement with our study when we considered the entire cohort together (Young et al., 2013). However, once we separated animals into HA and LA groups, the α7 receptor partial agonist encenicline clearly improved attention, vigilance and response inhibition in LA animals. There are two key differences between the work of Young et al. (2013) and the present study; firstly, the model used in our study is a behavioural separation, whereas Young et al. (2013) used a pharmacologically-mediated deficit. Scopolamine has a number of non-specific effects, which may also affect performance, such as increased locomotor activity, pupil dilation and mnemonic changes (Klinkenberg and Blokland, 2010). The second difference is the mechanism of action of PNU-282987, which is a full agonist, whereas encenicline is a partial agonist, allowing it to act as an agonist or antagonist, depending on endogenous acetylcholine levels (Prickaerts et al., 2012; Hajos et al., 2005). Furthermore, as outlined earlier, other α7 nAChR partial agonists have been shown to improve attention (Rezvani et al., 2009; Haig et al., 2016; Shiina et al., 2010), but have not been tested in specific tasks of attention/ vigilance and not in animals separated according to performance.

In a small study of schizophrenia patients, encenicline added onto regular medication had no effect on the attentive measures in the CogState schizophrenia battery compared to placebo (Preskorn et al., 2014). The small sample size in this study where the placebo group composed of 4 patients was a serious limitation and the authors recommend caution for these measures. Indeed, a larger study, using the same doses found significant effects of encenicline across a broad range of cognitive tests, including attention, using the CogState battery (Keefe et al., 2015). In a small pilot study in schizophrenia patients both mismatch negativity (a negative potential following an odd stimulus in a sequence) and P300 (positive inflection after a standard stimulus presentation) which can be correlated to the severity of cognitive deficits (Ford et al., 1999; Baldeweg et al., 2004) were shown to be normalised by encenicline (Preskorn et al., 2014). However, a recent phase III trial did not reach significance for primary cognitive endpoints in schizophrenia patients compared to placebo (Pharmaceuticals, 2016). Also, in the Alzheimer's disease Phase III trial, rare, but serious, gastrointestinal side effects have put testing on hold (Pharmaceuticals, 2015). These findings suggest that encenicline itself is not likely to be used clinically in either of these conditions, perhaps due to specific properties of the molecule, rather than the target itself.

Our data and other studies suggest that the α7 receptor is a valuable target for improving attention in disorders where this is impaired, and supports efforts to find a clinically-viable molecule. Development is still on-going for new α7 partial agonists which may prove more successful (Bristow et al., 2016). An alternative route of investigation is the

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positive allosteric modulators of the α7 receptor, but these have yet to be tested in attention tasks. It is important to note that no drug has yet received a license specifically for improving cognition in schizophrenia; this is clearly a particularly challenging unmet clinical need. In our view, it is most likely that pharmacological combined with psychological and other interventions, such as cognitive remediation and exercise therapy, providing a holistic approach to treatment is most likely to produce positive effects for this symptom domain and improve quality of life for patients.

In summary, this study demonstrates that separation by performance in the 5C-CPT is feasible using a variable SD. The difference in performance was greatest when the animals were most challenged; in this case with a 0.75 s SD. Encenicline showed contrasting effects on attention and vigilance in LA and HA animals. In LA animals, encenicline improves selective attention, vigilance and response inhibition (impulsive action), but in HA animals selective attention and vigilance are reduced. These findings show for the first time, that an α7 nAChR partial agonist improves attention when tested in a specific task of attention designed for high translation (5C-CPT) and that this depends on baseline levels of attention. Our data suggests that partial agonism at the α7 nAChR has the potential to enhance attention in patients stratified according to low attentional performance.

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Contributors

AH was involved in experimental design, conducted the experiments, data analysis and preparation of the manuscript. LA assisted with experimental procedures, in particular training of animals. JCN conceived the study with AH, supervised the study, was involved in experimental design, data analysis and manuscript preparation. All authors have approved the manuscript.

Conflicts of interest

JCN has received honoraria for lecturing and consultancy work and serves on the advisory boards of several pharmaceutical companies. She is a full-time employee of the University of Manchester. LA was an employee of b-neuro at the University of Manchester at the time these experiments were conducted. AH is a PhD student funded by b-neuro and Manchester Pharmacy School. Autifony Therapeutics provided the compound for testing, but were not involved in design or implementation of the experiment and took no part in preparing the manuscript.

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References

Arnsten, A.F., 2009. Toward a new understanding of attention-deficit hyperactivity disorder pathophysiology: an important role for prefrontal cortex dysfunction. CNS Drugs 23 (Suppl 1), S33–S41.

Baldeweg, T., Klugman, A., Gruzelier, J., Hirsch, S.R., 2004. Mismatch negativity potentials and cognitive impairment in schizophrenia. Schizophr. Res. 69, 203–217.

Barnes, S.A., Young, J.W., Neill, J.C., 2012a. D-1 receptor activation improves vigilance in rats as measured by the 5-choice continuous performance test. Psychopharmacology 220, 129–141.

Barnes, S.A., Young, J.W., Neill, J.C., 2012b. Rats tested after a washout period from sub-chronic PCP administration exhibited impaired performance in the 5-Choice Continuous Performance Test (5C-CPT) when the attentional load was increased. Neuropharmacology 62, 1432–1441.

Bloem, B., Poorthuis, R.B., Mansvelder, H.D., 2014. Cholinergic modulation of the medial prefrontal cortex: the role of nicotinic receptors in attention and regulation of neuronal activity. Front Neural Circuits 8, 17.

Blondeau, C., Dellu-Hagedorn, F., 2007. Dimensional analysis of ADHD subtypes in rats. Biol. Psychiatry 61, 1340–1350.

Brioni, J.D., Kim, D.J., O'neill, A.B., 1996. Nicotine cue: lack of effect of the alpha 7 nicotinic receptor antagonist methyllycaconitine. Eur. J Pharmacol. 301, 1–5.

Bristow, L.J., Easton, A.E., Li, Y.W., Sivarao, D.V., Lidge, R., Jones, K.M., Post-Munson, D., Daly, C., Lodge, N.J., Gallagher, L., Molski, T., Pieschl, R., Chen, P., Hendricson, A., Westphal, R., Cook, J., Iwuagwu, C., Morgan, D., Benitex, Y., King, D., Macor, J.E., Zaczek, R., Olson, R., 2016. The novel, nicotinic alpha7 receptor partial agonist, BMS-933043, improves cognition and sensory processing in preclinical models of schizophrenia. PLoS One 11, e0159996.

Brown, K.J., Grunberg, N.E., 1995. Effects of housing on male and female rats: crowding stresses male but calm females. Physiol. Behav. 58, 1085–1089.

Clark, R.A., Shoaib, M., Hewitt, K.N., Stanford, S.C., Bate, S.T., 2012. A comparison of InVivoStat with other statistical software packages for analysis of data generated from animal experiments. J. Psychopharmacol. 26, 1136–1142.

Dalley, J.W., Fryer, T.D., Brichard, L., Robinson, E.S., Theobald, D. E., Laane, K., Pena, Y., Murphy, E.R., Shah, Y., Probst, K., Abakumova, I., Aigbirhio, F.I., Richards, H.K., Hong, Y., Baron, J. C., Everitt, B.J., Robbins, T.W., 2007. Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. Science 315, 1267–1270.

Foldi, N.S., Lobosco, J.J., Schaefer, L.A., 2002. The effect of attentional dysfunction in Alzheimer's disease: theoretical and practical implications. Semin Speech Lang. 23, 139–150.

Ford, J.M., Mathalon, D.H., Marsh, L., Faustman, W.O., Harris, D., Hoff, A.L., Beal, M., Pfefferbaum, A., 1999. P300 amplitude is related to clinical state in severely and moderately ill patients with schizophrenia. Biol. Psychiatry 46, 94–101.

Grottick, A.J., Higgins, G.A., 2000. Effect of subtype selective nicotinic compounds on attention as assessed by the five-choice serial reaction time task. Behav. Brain Res. 117, 197–208.

Haig, G.M., Bain, E.E., Robieson, W.Z., Baker, J.D., Othman, A.A., 2016. A Randomized Trial to Assess the Efficacy and Safety of

ABT-126, a Selective alpha7 Nicotinic Acetylcholine Receptor Agonist, in the Treatment of Cognitive Impairment in Schizophrenia. Am. J Psychiatry (appiajp201515010093).

Hajos, M., Hurst, R.S., Hoffmann, W.E., Krause, M., Wall, T.M., Higdon, N.R., Groppi, V.E., 2005. The selective alpha7 nicotinic acetylcholine receptor agonist PNU-282987 [N-[(3R)-1-Azabicyclo[2.2.2]oct-3-yl]-4-chlorobenzamide hydrochloride] enhances GABAergic synaptic activity in brain slices and restores auditory gating deficits in anesthetized rats. J Pharmacol. Exp. Ther. 312, 1213–1222.

Hayward, A., Tomlinson, A., Neill, J.C., 2016. Low attentive and high impulsive rats: a translational animal model of ADHD and disorders of attention and impulse control. Pharmacol. Ther. 158, 41–51.

Heishman, S.J., Kleykamp, B.A., Singleton, E.G., 2010. Meta-analysis of the acute effects of nicotine and smoking on human performance. Psychopharmacol. (Berl.) 210, 453–469.

Holson, R.R., Scallet, A.C., Ali, S.F., Turner, B.B., 1991. "Isolation stress" revisited: isolation-rearing effects depend on animal care methods. Physiol. Behav. 49, 1107–1118.

Hoyle, E., Genn, R.F., Fernandes, C., Stolerman, I.P., 2006. Impaired performance of alpha7 nicotinic receptor knockout mice in the five-choice serial reaction time task. Psychopharmacol. (Berl.) 189, 211–223.

Huang, M., Felix, A.R., Flood, D.G., Bhuvaneswaran, C., Hilt, D., Koenig, G., Meltzer, H.Y., 2014. The novel alpha7 nicotinic acetylcholine receptor agonist EVP-6124 enhances dopamine, acetylcholine, and glutamate efflux in rat cortex and nucleus accumbens. Psychopharmacol. (Berl.).

Keefe, R.S., Meltzer, H.A., Dgetluck, N., Gawryl, M., Koenig, G., Moebius, H.J., Lombardo, I., Hilt, D.C., 2015. Randomized, double-blind, placebo-controlled study of encenicline, an alpha7 nicotinic acetylcholine receptor agonist, as a treatment for cognitive impairment in schizophrenia. Neuropsychopharmacology 40, 3053–3060.

Klinkenberg, I., Blokland, A., 2010. The validity of scopolamine as a pharmacological model for cognitive impairment: a review of animal behavioral studies. Neurosci. Biobehav Rev. 34, 1307–1350.

Kolisnyk, B., Al-Onaizi, M.A., Prado, V.F., Prado, M.A., 2015. alpha7 nicotinic ACh receptor-deficient mice exhibit sustained attention impairments that are reversed by beta2 nicotinic ACh receptor activation. Br. J Pharmacol. 172, 4919–4931.

Luck, S.J., Gold, J.M., 2008. The construct of attention in schizophrenia. Biol. Psychiatry 64, 34–39.

Lustig, C., Kozak, R., Sarter, M., Young, J.W., Robbins, T.W., 2013. CNTRICS final animal model task selection: control of attention. Neurosci. Biobehav Rev. 37, 2099–2110.

Mclean, S.L., Grayson, B., Idris, N.F., Lesage, A.S., Pemberton, D. J., Mackie, C., Neill, J.C., 2011. Activation of alpha7 nicotinic receptors improves phencyclidine-induced deficits in cognitive tasks in rats: implications for therapy of cognitive dysfunction in schizophrenia. Eur. Neuropsychopharmacol. 21, 333–343.

Mclean, S.L., Grayson, B., Marsh, S., Zarroug, S.H., Harte, M.K., Neill, J.C., 2016. Nicotinic alpha7 and alpha4beta2 agonists enhance the formation and retrieval of recognition memory: potential mechanisms for cognitive performance enhancement in neurological and psychiatric disorders. Behav. Brain Res. 302, 73–80.

Muir, J.L., Everitt, B.J., Robbins, T.W., 1995. Reversal of visual attentional dysfunction following lesions of the cholinergic basal forebrain by physostigmine and nicotine but not by the 5-HT3 receptor antagonist, ondansetron. Psychopharmacol. (Berl.) 118, 82–92.

Olincy, A., Freedman, R., 2012. Nicotinic mechanisms in the treatment of psychotic disorders: a focus on the alpha7 nicotinic receptor. Handb. Exp. Pharmacol., 211–232.

Parikh, V., Kutlu, M.G., Gould, T.J., 2016. nAChR dysfunction as a common substrate for schizophrenia and comorbid nicotine addiction: current trends and perspectives. Schizophr. Res 171, 1–15.

Pharmaceuticals, F., 2015. FORUM Pharmaceuticals Inc., Announces Removal of Partial Clinical Hold on Phase 3 Encenicline Program for Cognitive Impairment in Schizophrenia ⟨http://www.forumpharma.com/forum-pharmaceuticals-inc-announces-removal-of-partial-clinical-hold-on-phase-3-encenicline-program-for-cognitive-impairment-in-schizophrenia/⟩.

Pharmaceuticals, F., 2016. FORUM Pharmaceuticals Inc., Provides Update on Encenicline Phase 3 Clinical Trial Program in Cognitive Impairment in Schizophrenia In: HEINS, S. (Ed.). ⟨http://www.forumpharma.com/forum-pharmaceuticals-inc-provides-update-encenicline-phase-3-clinical-trial-program-cognitive-impairment-schizophrenia/⟩.

Picciotto, M.R., 2003. Nicotine as a modulator of behavior: beyond the inverted U. Trends Pharmacol. Sci. 24, 493–499.

Picciotto, M.R., Zoli, M., Rimondini, R., Lena, C., Marubio, L.M., Pich, E.M., Fuxe, K., Changeux, J.P., 1998. Acetylcholine receptors containing the beta2 subunit are involved in the reinforcing properties of nicotine. Nature 391, 173–177.

Poltavski, D.V., Petros, T., 2006. Effects of transdermal nicotine on attention in adult non-smokers with and without attentional deficits. Physiol. Behav. 87, 614–624.

Pons, S., Fattore, L., Cossu, G., Tolu, S., Porcu, E., Mcintosh, J.M., Changeux, J.P., Maskos, U., Fratta, W., 2008. Crucial role of alpha4 and alpha6 nicotinic acetylcholine receptor subunits from ventral tegmental area in systemic nicotine self-administration. J Neurosci. 28, 12318–12327.

Preskorn, S.H., Gawryl, M., Dgetluck, N., Palfreyman, M., Bauer, L. O., Hilt, D.C., 2014. Normalizing effects of EVP-6124, an alpha-7 nicotinic partial agonist, on event-related potentials and cognition: a proof of concept, randomized trial in patients with schizophrenia. J Psychiatr. Pract. 20, 12–24.

Prickaerts, J., VAN Goethem, N.P., Chesworth, R., Shapiro, G., Boess, F.G., Methfessel, C., Reneerkens, O.A., Flood, D.G., Hilt, D., Gawryl, M., Bertrand, S., Bertrand, D., Konig, G., 2012. EVP-6124, a novel and selective alpha7 nicotinic acetylcholine receptor partial agonist, improves memory performance by potentiating the acetylcholine response of alpha7 nicotinic acetylcholine receptors. Neuropharmacology 62, 1099–1110.

Rezvani, A.H., Levin, E.D., 2001. Cognitive effects of nicotine. Biol. Psychiatry 49, 258–267.

Rezvani, A.H., Kholdebarin, E., Brucato, F.H., Callahan, P.M., Lowe, D.A., Levin, E.D., 2009. Effect of R3487/MEM3454, a novel nicotinic alpha7 receptor partial agonist and 5-HT3 antagonist on sustained attention in rats. Prog. Neuropsychopharmacol. Biol. Psychiatry 33, 269–275.

Robbins, T.W., 2002. The 5-choice serial reaction time task: behavioural pharmacology and functional neurochemistry. Psychopharmacology 163, 362–380.

Segarra, R., Zabala, A., Eguiluz, J.I., Ojeda, N., Elizagarate, E., Sanchez, P., Ballesteros, J., Gutierrez, M., 2011. Cognitive performance and smoking in first-episode psychosis: the self-medication hypothesis. Eur. Arch. Psychiatry Clin. Neurosci. 261, 241–250.

Shiina, A., Shirayama, Y., Niitsu, T., Hashimoto, T., Yoshida, T., Hasegawa, T., Haraguchi, T., Kanahara, N., Shiraishi, T., Fujisaki, M., Fukami, G., Nakazato, M., Iyo, M., Hashimoto, K., 2010. A randomised, double-blind, placebo-controlled trial of tropisetron in patients with schizophrenia. Ann. Gen. Psychiatry 9, 27.

Tomlinson, A., Grayson, B., Marsh, S., Harte, M.K., Barnes, S.A., Marshall, K.M., Neill, J.C., 2014. Pay attention to impulsivity: modelling low attentive and high impulsive subtypes of adult ADHD in the 5-choice continuous performance task (5C-CPT) in female rats. Eur. Neuropsychopharmacol.

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Tomlinson, A., Grayson, B., Marsh, S., Hayward, A., Marshall, K.M., Neill, J.C., 2015. Putative therapeutic targets for symptom subtypes of adult ADHD: d4 receptor agonism and COMT inhibition improve attention and response inhibition in a novel translational animal model. Eur. Neuropsychopharmacol. 25, 454–467.

Van Goethem, N.P., Prickaerts, J., Welty, D., Flood, D.G., Koenig, G., 2015. Continuous infusion of the alpha7 nicotinic acetylcholine receptor agonist EVP-6124 produces no signs of tolerance at memory-enhancing doses in rats: a pharmacokinetic and behavioral study. Behav. Pharmacol. 26, 403–406.

Vizi, E.S., Lendvai, B., 1999. Modulatory role of presynaptic nicotinic receptors in synaptic and non-synaptic chemical communication in the central nervous system. Brain Res. Brain Res. Rev. 30, 219–235.

Watkins, S.S., Koob, G.F., Markou, A., 2000. Neural mechanisms underlying nicotine addiction: acute positive reinforcement and withdrawal. Nicotine Tob. Res. 2, 19–37.

White, H.K., Levin, E.D., 1999. Four-week nicotine skin patch treatment effects on cognitive performance in Alzheimer's disease. Psychopharmacol. (Berl.) 143, 158–165.

Wignall, N.D., DE Wit, H., 2011. Effects of nicotine on attention and inhibitory control in healthy nonsmokers. Exp. Clin. Psychopharmacol. 19, 183–191.

Wood, S., Sage, J.R., Shuman, T., Anagnostaras, S.G., 2014. Psychostimulants and cognition: a continuum of behavioral and cognitive activation. Pharmacol. Rev. 66, 193–221.

Young, J.W., Geyer, M.A., 2013. Evaluating the role of the alpha-7 nicotinic acetylcholine receptor in the pathophysiology and treatment of schizophrenia. Biochem. Pharmacol. 86, 1122–1132.

Young, J.W., Crawford, N., Kelly, J.S., Kerr, L.E., Marston, H.M., Spratt, C., Finlayson, K., Sharkey, J., 2007. Impaired attention is central to the cognitive deficits observed in alpha 7 deficient mice. Eur. Neuropsychopharmacol. 17, 145–155.

Young, J.W., Powell, S.B., Scott, C.N., Zhou, X., Geyer, M.A., 2011. The effect of reduced dopamine D4 receptor expression in the 5-choice continuous performance task: separating response inhibition from premature responding. Behav. Brain Res. 222, 183–192.

Young, J.W., Meves, J.M., Geyer, M.A., 2013. Nicotinic agonist-induced improvement of vigilance in mice in the 5-choice continuous performance test. Behav. Brain Res. 240, 119–133.

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