Published in final edited form as:

Neuroscience. 2013 January 29; 230: 121–131. doi:10.1016/j.neuroscience.2012.10.067.

$\alpha 4\beta 2^*$ and $\alpha 7$ Nicotinic Acetylcholine Receptor Binding Predicts Choice Preference in Two Cost Benefit Decision Making Tasks

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Abstract

Nicotinic receptors have been linked to a wide range of cognitive and behavioral functions, but surprisingly little is known about their involvement in cost benefit decision making. The goal of these experiments was to determine how nicotinic acetylcholine receptor (nAChR) expression is related to two forms of cost benefit decision making. Male Long Evans rats were tested in probability and delay discounting tasks, which required discrete trial choices between a small reward and a large reward associated with varying probabilities of omission and varying delays to reward delivery, respectively. Following testing, radioligand binding to $\alpha 4\beta 2^*$ and $\alpha 7$ nAChR subtypes in brain regions implicated in cost benefit decision making was examined. Significant linear relationships were observed between choice of the large delayed reward in the delay discounting task and $\alpha 4\beta 2^*$ receptor binding in both dorsal and ventral hippocampus. Additionally, trends were found suggesting that choice of the large costly reward in both discounting tasks was inversely related to $\alpha 4\beta 2^*$ receptor binding in the medial prefrontal cortex and nucleus accumbens shell. Similar, trends suggested that choice of the large delayed reward in the delay discounting task was inversely related to $\alpha 4\beta 2^*$ receptor binding in the orbitofrontal cortex, nucleus accumbens core, and basolateral amygdala, as well as to $\alpha 7$ receptor binding in basolateral amygdala. These data suggest that nAChRs (particularly $\alpha 4\beta 2^*$) play both unique and common roles in decisions that require consideration of different types of reward costs.

Keywords

delay discounting; probability discounting; nicotinic receptor; acetylcholine; rat; impulsivity

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1. Introduction

Cost benefit decision making is characterized by the ability to make choices among reward options for which the outcomes differ in both reward magnitudes and costs, the latter of which can include such variables as delay to reward delivery and probability of reward omission. Optimal cost benefit decision making yields maximum rewards with minimum costs, whereas poor cost benefit decision making (termed “impulsive” in the case of suboptimal delay based decision making and “risky” in the case of suboptimal probability based decision making) results in larger costs and/or smaller rewards. Over the last 15 years, much has been learned about the pharmacological basis of cost benefit decision making (see Cardinal, 2006; Floresco et al., 2008; Pattij and Vanderschuren, 2008 for reviews). Largely absent from this literature, however, is information concerning the involvement of cholinergic systems.

The lack of knowledge about the role of cholinergic systems in cost benefit decision making is surprising given that cholinergic signaling has been implicated in psychological processes necessary for cost benefit decision making, including attention, learning and memory, and motivation, particularly for rewards and reward related cues (Hoebel et al., 2007; Robbins and Roberts, 2007; Kenney and Gould, 2008; Hasselmo and Sarter, 2011). Additionally, there is limited evidence from studies in rodents and humans that pharmacological modulation of nicotinic acetylcholine receptors (nAChRs) can shift choice preference in tasks that assess cost benefit decision making (Mitchell, 2004; Reynolds et al., 2004; Dallery and Locey, 2005; Kolokotroni et al., 2011; Mendez et al., 2012; Xie et al., 2012). Finally, cholinergic signaling has been implicated in the etiology and/or treatment of numerous neuropsychiatric conditions in which cost benefit decision making is altered, including schizophrenia, Alzheimer’s disease, attention deficit hyperactivity disorder (ADHD), Parkinson’s disease, and addiction (Clark and Robbins, 2002; Kalivas and Volkow, 2005; Karlawish et al., 2005; Thompson et al., 2007; Williams and Adinoff, 2008; Euteneuer et al., 2009; Weiler et al., 2009; Gleichgerricht et al., 2010). These relationships are complemented by human studies using radioligand binding to assess nAChR density in patients with schizophrenia and Alzheimer’s disease. Patients with these disorders show decreased post-mortem levels of the heteromeric $\alpha 4\beta 2^*$ nAChR subtype in both striatum and cortex when compared to controls (Flynn and Mash, 1986; Warpman and Nordberg, 1995; Breese et al., 2000; Durany et al., 2000). Similarly, post-mortem analysis of individuals diagnosed with schizophrenia shows decreased levels of the homomeric $\alpha 7$ nAChR subtype within the prefrontal cortex (Guan et al., 1999).

The current study was designed to address this gap in the literature, by determining the relationships between cost benefit decision making and radioligand binding to $\alpha 4\beta 2^*$ and $\alpha 7$ nAChRs across multiple brain regions in adult male rats. These analyses took advantage of the reliable and stable individual differences in cost benefit decision making that are observed in rats, which allow correlations between neurobiological and behavioral measures to be conducted (Loos et al., 2010; Simon et al., 2011). In addition, two forms of cost benefit decision making were examined: “impulsive” decision making, as assessed using a delay discounting task, and “risky” decision making, as assessed using a probability discounting task (Evenden and Ryan, 1996; Cardinal and Howes, 2005; Floresco et al., 2008; Mendez et al., 2010).

2. Experimental Procedures

2.1. Subjects

The subjects were male Long Evans rats ($n = 16$) weighing 250 to 275 g upon arrival (Charles River Laboratories, Wilmington, NC, USA). Rats were housed individually in a

climate controlled vivarium (25°C) at Texas A&M University. Rats had food and water freely available except as noted below. Testing took place during the light cycle of a 12 hr light/dark schedule (lights on 0800 to 2000 hrs), and was conducted according to the “Principles of Laboratory Animal Care” (National Academy of Sciences, USA) and NIH and institutional animal care and use guidelines. Rats were allowed to acclimate to vivarium conditions for at least one week before the start of experiments. Prior to testing in the discounting tasks, rats were food restricted to 85% of their free feeding weight over the course of 5 days. In order to maintain the rats at this weight during behavioral testing, food was limited to 15 grams per day (in addition to food rewards earned during the tasks), with allowances for growth. Upon completion of behavioral testing, rats were returned to a free feeding schedule.

2.2. Behavioral Apparatus

Decision making was assessed in eight identical standard rat behavioral test chambers (31 × 25 × 31 cm) located in sound attenuating cubicles (Coulbourn Instruments, Whitehall, PA). Each chamber had aluminum front and back walls, acrylic side walls, and a floor composed of steel rods (0.4 cm diameter, spaced 1.1 cm apart). A recessed food trough (4.1 × 3.2 cm) into which grain based food pellet rewards (PJAI, Test Diet, 45 mg) were delivered was equipped with a photobeam to detect head entries and a 1.12 watt trough light, and was located in the center of the front wall of each chamber (2.2 cm above the floor). Retractable response levers were located on each side of the food trough (11 cm above the floor), and they were extended and withdrawn as described in the task protocols below. Locomotor activity was detected by activity monitors with infrared detectors mounted on the ceilings of the test chambers. The chambers were interfaced with a computer running Graphic State 3.01 software (Coulbourn Instruments) to control stimulus deliveries and record data.

2.3. Behavioral Protocols

2.3.1. Probability Discounting Task—The day before training in the task began rats were given five 45 mg food pellets in their home cages to reduce neophobia to the food rewards used in the task. Shaping began with a 64 min session of magazine training consisting of 38 deliveries of a single food pellet with an intertrial interval (ITI) of 100 ± 40 sec. On the following day, rats were shaped to press a single lever (either left or right, balanced across rats; the other was retracted during this phase of training) in order to receive a single food pellet. Once they reached a criterion of 50 lever presses during a 30 min session, they were shaped to press the opposite lever using the same schedule and criterion. Following completion of lever press shaping, both levers were retracted, and rats were shaped to nose poke into the food trough during simultaneous illumination of the trough light and a 1.12 watt house light mounted on the rear wall of the isolation cubicle. When a nose poke occurred, a single lever was extended, and a lever press resulted in immediate delivery of a single food pellet. Immediately following the lever press, the house and trough lights were extinguished and the lever was retracted. The left and right levers were presented an equal number of times, with no more than two consecutive presentations of the same lever. Rats were trained to a criterion of at least 60 successful trials in 1 hr with an ITI of 40 ± 10 sec, after which testing on the probability discounting task began.

Test sessions in the probability discounting task were conducted once per day. Each session was 60 min long and consisted of five blocks of 18 trials each. Each 40 sec trial began with a 10 sec illumination of the food trough and house lights. A nose poke into the food trough during this time extinguished the food trough light and triggered extension of either a single lever (forced choice trials) or both levers simultaneously (free choice trials) for 10 sec. Trials on which rats failed to nosepoke during this time window were scored as omissions. A press on one lever (either left or right, balanced across rats) resulted in immediate delivery

of a single food pellet (the small reward). A press on the other lever resulted in immediate delivery of four food pellets (the large reward). Failures to press either lever were scored as omissions. During the first block of trials, the large reward was delivered with 100% probability following selection of the large reward lever. During each of the four subsequent blocks, the probability of large reward delivery was systematically decreased (50, 25, 12.5 and 0%). Each 18 trial block began with eight forced choice trials (4 for each lever) used to expose the rats to the reward probabilities in effect for that block, followed by 10 free choice trials (Cardinal and Howes, 2005; Simon et al., 2009). Once either lever was pressed, both levers were immediately retracted. Food delivery was accompanied by illumination of both the food trough and house lights, which were extinguished upon entry to the food trough to collect the food or after 10 sec, whichever occurred first. Rats were tested in the probability discounting task until stable performance (as described in section 2.5) was achieved, at which point they were switched to the delay discounting task.

2.3.2. Delay Discounting Task—This task was similar in design to the probability discounting task, and hence no further shaping sessions were required. Each 60 min session consisted of 5 blocks of 12 trials each. Each 60 sec trial began with a 10 sec illumination of the food trough and house lights. A nose poke into the food trough during this time extinguished the food trough light and triggered extension of either a single lever (forced choice trials) or of both levers simultaneously (free choice trials). Each block consisted of 2 forced choice trials used to expose the rats to the delays in effect for that block, followed by 10 free choice trials. A press on one lever (either left or right, balanced across rats) resulted in one food pellet (the small reward) delivered immediately. A press on the other lever resulted in three food pellets (the large reward) delivered after a variable delay. Once either lever was pressed, both levers were retracted for the remainder of the trial. The delay duration increased between each block of trials (0, 4, 8, 16, 32 sec), but remained constant within each block (Evenden and Ryan, 1996; Winstanley et al., 2006; Mitchell et al., 2012). Rats were tested in the delay discounting task until stable performance was achieved.

2.4. Radioligand Binding

Radioligand binding was used to determine nAChR levels in brain regions associated in previous work with risky and impulsive decision making. Three days following completion of all behavioral testing, rats were deeply anesthetized with inhaled isoflurane and sacrificed for brain harvesting. Collected brains were immediately frozen at -30°C in isopentane for 60 sec, and stored at -80°C until slicing. Twenty micrometer thick coronal brain sections were collected on a cryostat at -18°C through cortical (orbitofrontal, medial prefrontal, cingulate, and agranular insular cortex) and subcortical (dorsal striatum, nucleus accumbens shell and core, basolateral amygdala, dorsal and ventral hippocampus, and ventral tegmental area) regions, and mounted onto Superfrost plus slides (VWR, USA). Slides were kept on ice during cutting, then desiccated overnight at 4°C and temporarily stored at -80°C . Using receptor autoradiography, nAChR subtype levels were identified using iodinated radioligands. [^{125}I] epibatidine (specific radioactivity 2200 Ci/mmol, Amersham, UK) was used at a concentration of 0.4 nM to identify the $\alpha 4\beta 2^*$ nAChR subtype, and [^{125}I] α bungarotoxin (specific radioactivity 150 Ci/mmol, Amersham, UK) was used at a concentration of 5 nM to identify the $\alpha 7$ nAChR subtype (Huang and Winzer-Serhan, 2006). Tissue sections were incubated in fresh Tris HCl buffer solution (50 mM Tris HCl base, 120 mM NaCl, 5 mM KCl, 2.5 mM CaCl_2 , and 1 mM MgCl_2 , adjusted to pH 7.4 with 10 N HCl) for 5 min. For total binding, sections were incubated within the Tris HCl buffer at room temperature for 60 min. Adjacent sections designated for nonspecific binding were processed in the presence of 100 μM nicotine hydrogen tartrate (Sigma Aldrich Inc, USA), which was added to pre incubation and incubation buffers. Following incubation, sections were washed in ice cold incubation buffer twice for 5 min each, followed by ice cold ddH_2O

for 30 sec, dried under constant airflow for 1 hr at room temperature and exposed to film (Kodak Biomax MR Film) for several days (2 days for epibatidine, 3 days for α bungarotoxin) along with [125 I] standards of known radioactivity. Films were developed in D19 Kodak developer for 4 min, rinsed in water, and fixed in Kodak Rapid Fixer for 5 min. Images from [125 I] epibatidine autoradiograms and [125 I] α bungarotoxin autoradiograms were quantitatively analyzed using a PC-based image analysis system (InterFocus Imaging Ltd., UK). A calibration curve of radioactivity (nCi/mg tissue versus optical density) was generated using the [125 I] standards.

2.5. Statistical Analysis

Raw behavioral data files were exported from Graphic State software and compiled using a custom macro written for Microsoft Excel (Dr. Jonathan Lifshitz, University of Kentucky). Statistical analyses were conducted in SPSS 16.0. Stable performance in the discounting tasks was determined using a two way repeated measures ANOVA (session $\times$ probability/delay) conducted on data (% choice of the large reward in each trial block) from 5 consecutive sessions. Stability was defined by the absence of a main effect or interaction involving session, accompanied by a significant main effect of probability or delay (Cardinal et al., 2000; Winstanley et al., 2006; Mendez et al., 2010). To determine relationships between performance in the discrimination tasks and receptor binding measures, data were averaged across the 5 sessions of stable behavior and across the 5 trial blocks to obtain a single value for each rat (mean % choice of the large reward) in each discounting task. The number of shaping sessions required to achieve criterion was also calculated for each rat and used as a measure of learning. Two-tailed Pearson's bivariate correlations were used to determine linear relationships between these values and binding measures in each brain region. Because of the large number of correlations, a Bonferroni correction procedure was used to identify relationships that could be determined with confidence and those that should be interpreted with caution.

3. Results

3.1. Behavioral performance in the delay and probability discounting tasks

Rats were trained in each task until stable performance was achieved (35 sessions in the probability discounting task, and 20 sessions in the delay discounting task). Both group and individual rat performance in each task, averaged across the last 5 sessions of testing (during which stability was achieved) are shown in Figure 1. Following behavioral testing, rats were sacrificed and brains were collected for receptor binding analyses.

3.2. Relationships between performance in the delay and probability discounting tasks and nicotinic receptor radioligand binding

Autoradiographic images of $\alpha 4\beta 2^*$ (Figure 2) and $\alpha 7$ (Figure 3) radioligand binding were analyzed across brain regions. Relationships between binding and performance in the discounting tasks (mean % choice of the large reward) were assessed using Pearson's bivariate correlations (Table 1). It should be noted that although binding levels within many regions in the brain did not reach significance based on the Bonferroni-adjusted, stricter critical value, there were many more correlations below a .05 critical value than would be predicted to occur by chance. Hence, although they should be interpreted with caution, all correlations that reached the .05 critical value are described below.

The most robust relationships between discounting performance and nAChR binding (and the only ones that reached the Bonferroni-adjusted critical value) were negative correlations between performance in the delay discounting task and $\alpha 4\beta 2^*$ nAChR density levels in both the ventral ($r = -.83$, $p < .001$, Figure 4(A)) and dorsal ($r = -.87$, $p < .001$, Figure 4(B))

hippocampus, such that as preference for the large delayed reward increased, density levels decreased. In addition, there were trends toward negative correlations between performance in the delay discounting task and $\alpha 4\beta 2^*$ nAChR density levels in the orbitofrontal ($r = -.56$, $p = .039$, Figure 5(A)) and medial prefrontal ($r = -.56$, $p = 0.036$, Figure 5(B)) cortex, as well as between performance in the probability discounting task and $\alpha 4\beta 2^*$ nAChR density levels in the medial prefrontal cortex ($r = -.58$, $p = .031$, Figure 5(C)), such that as preference for the large reward increased, $\alpha 4\beta 2^*$ nAChR density levels in these regions decreased. Additional trends toward negative correlations were observed between performance in the delay discounting task and $\alpha 4\beta 2^*$ nAChR density levels in the nucleus accumbens core ($r = -.73$, $p = .004$, Figure 6(A)) and shell ($r = -.64$, $p = .018$, Figure 6(B)), and between performance in the probability discounting task and $\alpha 4\beta 2^*$ nAChR density levels in the nucleus accumbens shell ($r = -.61$, $p = .028$, Figure 6(C)). Finally, a trend toward a negative correlation was observed between performance in the delay discounting task and $\alpha 4\beta 2^*$ nAChR density levels in the basolateral amygdala ($r = -.61$, $p = .045$, Figure 7(A)).

Compared to $\alpha 4\beta 2^*$ density, relationships between $\alpha 7$ nAChR density levels and performance in the delay and probability discounting tasks were much less robust (Table 1). In the delay discounting task, there was a trend toward a negative correlation between $\alpha 7$ nAChR density levels and task performance only in the basolateral amygdala ($r = -.54$, $p = .039$), such that greater preference for the large delayed reward was associated with lower $\alpha 7$ nAChR density levels in this region (Figure 7(B)). Performance in the probability discounting task was not associated with $\alpha 7$ nAChR density levels in any brain region analyzed (Table 1). Finally, the only relationship observed between the number of shaping sessions to reach criterion and any of the binding measures was a trend toward a negative correlation with $\alpha 7$ nAChR levels in OFC, such that a greater number of shaping sessions was associated with less binding ($r = -.52$, $p = .049$).

4. Discussion

Although the involvement of several neurotransmitter systems in cost benefit decision making is reasonably well understood, there has been much less information concerning the role of the cholinergic system (Pattij and Vanderschuren, 2008; Perry and Carroll, 2008). The results of this experiment suggest possible roles for the two major central nicotinic receptor subtypes ($\alpha 4\beta 2^*$ and $\alpha 7$) in probability and delay discounting. The relationships between nAChR (particularly $\alpha 4\beta 2^*$) binding and choice behavior showed considerable consistency across the two discounting tasks, in that, across multiple brain regions, higher levels of nicotinic receptor binding were associated with lower preference for the large reward. The fact that this relationship was evident across both tasks (particularly in the trends with $\alpha 4\beta 2^*$ receptor binding in medial prefrontal cortex and nucleus accumbens shell) suggests that activity at these receptors influenced choice behavior through common mechanisms.

Acute activation of both nAChR subtypes has been shown to affect a number of processes important for cost benefit decision making, including learning and memory, attention, and reward (Alkondon et al., 1992; Alkondon and Albuquerque, 1995; Granon et al., 1995; Foulds et al., 1996; Witte et al., 1997; Chan et al., 2007; Castner et al., 2010). Considering the possible mechanisms through which nicotinic receptor activation could influence choice behavior, effects on sensitivity to reward magnitude would appear to be a likely candidate. Acute systemic administration of nicotine results in reduced sensitivity to differences in reward magnitude, which would be expected to reduce preference for large costly rewards (Dallery and Locey, 2005; Locey and Dallery, 2011). Furthermore, research from other labs has suggested individual differences in sensitivity to reward magnitude as a contributor to

individual differences in risky decision making in rats (Rivalan et al., 2009). Hence, the associations observed here between higher nicotinic binding levels and lower preference for large rewards (either delayed or probabilistic) could be due to individual differences in nAChR-mediated sensitivity to reward magnitude. Notably, acute administration of nicotine causes reduced preference for large rewards in another cost benefit decision making task in which rats choose between a small “safe” reward and a large reward associated with risk of explicit punishment (Mitchell et al., 2011); (although see Anderson and Diller, 2010).

Although the brain regions in which greater nAChR binding was associated with (or trended toward associations with) reduced preference for large rewards (hippocampus, prefrontal cortex, nucleus accumbens, and basolateral amygdala) have all been implicated in probability and/or delay discounting (Winstanley et al., 2004; Cardinal and Howes, 2005; Churchwell et al., 2009; Mariano et al., 2009; St. Onge and Floresco, 2010; Finger et al., 2011), the roles of cholinergic activity within these brain regions in cost benefit decision making are as of yet unclear. Studies in smokers show long term increases in $\alpha 4\beta 2^*$ nAChR levels within the frontal cortex and striatum compared to non smoking controls (Breese et al., 1997; Court et al., 1998; Mukhin et al., 2008). These higher levels of nAChR binding in smokers, who also tend to show decreased preference for large delayed rewards (Bickel et al., 1999; Mitchell, 1999; Reynolds et al., 2004), are consistent with the negative relationships observed here between preference for large delayed reward and nAChR levels. Research with animals also supports these findings, as chronic nicotine administration results in both increases in cortical and striatal radioligand binding to $\alpha 4\beta 2^*$ nAChRs and decreased choice of large delayed rewards (Marks et al., 1987; Collins et al., 1989; Dallery and Locey, 2005). Although the effects of chronic nicotine on probability discounting are less clear (Mitchell, 1999; Reynolds et al., 2004), the current findings suggest a link between high levels of $\alpha 4\beta 2^*$ nAChR expression and decreased choice of large probabilistic rewards as well (although see Mendez et al., 2012).

The most robust inverse relationships between binding and behavioral data (and the only ones which were significant using Bonferroni-adjusted critical values) were in the hippocampus. The reasons for the strength of this relationship in hippocampus are not entirely clear (although $\alpha 4\beta 2^*$ receptors are expressed at high levels in this structure); however, in monkeys, low levels of $\alpha 4\beta 2^*$ nAChR binding in the hippocampus are associated with higher breakpoints on a progressive ratio schedule of responding for intravenous nicotine. It may be the case then that reduced hippocampal $\alpha 4\beta 2^*$ nAChR activity promotes the ability to wait for reward in both delay discounting and progressive ratio tasks (Le Foll et al., 2009). Interestingly, despite the strength of the relationship between hippocampal $\alpha 4\beta 2^*$ binding and delay discounting performance, this relationship was absent in the probability discounting task. This distinction suggests that hippocampal nicotinic cholinergic activity plays a more important role in decisions involving delayed than probabilistic rewards, although it is important to note that the smaller degree of variance in performance in the probability discounting task likely reduced the ability to detect correlations with nicotinic receptor binding.

Elevated cholinergic activity within nucleus accumbens is associated with reductions in food intake (Hoebel et al., 2007), suggesting a possible link between higher levels of $\alpha 4\beta 2^*$ nAChR binding in this region and reduced preference for large rewards. In addition, it should be noted that the finding of trends toward negative relationships between mPFC and nucleus accumbens shell (but not core) and probability discounting is consistent with recent evidence that these regions are specifically involved in probability discounting (St. Onge and Floresco, 2010; Stopper and Floresco, 2011). Finally, the fact that the vast majority of relationships between nAChR binding and task performance were observed with $\alpha 4\beta 2^*$ binding suggests that $\alpha 4\beta 2^*$ nAChRs may play a more prominent role than $\alpha 7$ nAChRs in

modulating cost benefit decision making. Indeed, in brain the $\alpha 4\beta 2^*$ nAChR subtype is associated with release of dopamine and norepinephrine (both of which strongly modulate cost benefit decision making, Pattij and Vanderschuren, 2008) in most brain regions and predominates in density and distribution (Picciotto et al., 1998; Perry et al., 2002; Granon et al., 2003; Woodruff-Pak et al., 2008; Le Foll et al., 2009), whereas the $\alpha 7$ nAChR subtype comprises only about 10% of all nAChRs (Young et al., 2004; Keller et al., 2005; Curzon et al., 2006; Hoyle et al., 2006; see Figures 2 and 3).

Conclusions

Although the involvement of several neurotransmitter systems in cost benefit decision making has been thoroughly investigated, there has been relatively much less research concerning the role of the cholinergic system (Pattij and Vanderschuren, 2008; Perry and Carroll, 2008). The results of this experiment suggest possible roles for the two major central nicotinic receptor subtypes ($\alpha 4\beta 2^*$ and $\alpha 7$) in probability and delay discounting. The relationships between nAChR (particularly $\alpha 4\beta 2^*$) binding and choice behavior showed considerable consistency across the two discounting tasks. Similar trends were observed across multiple brain regions, in that higher levels of nicotinic receptor binding were associated with lower preference for the large, costly reward. The fact that these trends were evident across both tasks (particularly with $\alpha 4\beta 2^*$ receptor binding in medial prefrontal cortex and nucleus accumbens shell) suggests that activity at these receptors may influence choice behavior through common mechanisms. Importantly, however, the design of the current experiment (such that receptor binding was assessed following behavioral testing) cannot rule out the possibility that the individual differences in receptor expression resulted from differential experiences in the discounting tasks (e.g., different amounts of food delivery or differential experiences with reward omission). Future experiments employing site-specific microinjections of $\alpha 4\beta 2^*$ and $\alpha 7$ nicotinic receptor ligands will help to address such questions of causality.

The findings concerning nAChR subtypes and cost benefit decision making may be of clinical interest, as these receptors are a target in several conditions which prominently feature alterations in cost benefit decision making, including ADHD, addiction, and Parkinson's disease (Kelton et al., 2000; Potter et al., 2006; Zanetti et al., 2006; Nakamura et al., 2007; McKee et al., 2009). The results of the current experiments suggest that $\alpha 4\beta 2^*$ and $\alpha 7$ nicotinic receptors are differentially involved in cost benefit decision making. Given the diversity of receptor subtypes through which drugs targeting nAChRs can act, it will be important to more directly determine the roles of these (and other) subtypes in different aspects of cost benefit decision making (for example, by employing nAChR subtype-specific ligands, and direct microinjections of such ligands into specific brain regions). Ultimately, such research may prove useful for guiding development of novel therapeutics for a wide range of neuropsychiatric conditions.

Acknowledgments

We thank Dr. Marci R. Mitchell and Colin M. Vokes for their assistance with this project. Supported by NIH grants MH65728 (IAM), AG02942 (JLB), and DA024671 (BS).

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- Examined relationships between decision-making and nicotinic receptor binding
- Choice of large delayed rewards inversely related to $\alpha 4\beta 2$ binding in hippocampus
- Data suggest that nAChRs in several brain regions involved in decision making

Figure 1.

Average performance across the last 5 days of testing in the probability and delay discounting tasks. (A) Group mean percent choice of the large reward in the probability discounting task. (B) Individual rats' percent choice of the large reward in the probability discounting task (each line represents data from a single rat). (C) Group mean percent choice of the large reward in the delay discounting task. (D) Individual rats' percent choice of the large reward in the delay discounting task.

Figure 2.

Representative receptor autoradiographic images of [125 I] epibatidine binding to $\alpha 4\beta 2^*$ nAChR in 20 μ m thick coronal brain sections at the level of prefrontal cortex (A), striatum (B), dorsal (C), and ventral (D) hippocampus. Abbreviations: orbitofrontal OFC, medial prefrontal mPFC, cingulate CC, and agranular insular AIC cortex, dorsal striatum dSTR, nucleus accumbens core NAcC and shell NAcS, dorsal hippocampus dHipp, basolateral amygdala BLA, ventral hippocampus vHipp, and ventral tegmental area VTA.

Figure 3.

Representative receptor autoradiographic images of [^{125}I] α bungarotoxin binding to $\alpha 7$ nAChR in 20 μm thick coronal brain sections at the level of prefrontal cortex (A), striatum (B), dorsal (C), and ventral (D) hippocampus. Abbreviations: orbitofrontal OFC, medial prefrontal mPFC, cingulate CC, and agranular insular AIC cortex, dorsal striatum dSTR, nucleus accumbens core NAcC and shell NAcS, dorsal hippocampus dHipp, basolateral amygdala BLA, ventral hippocampus vHipp, and ventral tegmental area VTA.

Figure 4.

Scatter plots and regression lines showing relationships ($p < .001$) between rats' percent choice of the large reward in the delay discounting task and $\alpha 4\beta 2^*$ nAChR binding density in hippocampus. An inverse relationship was found between preference for the large delayed reward in the delay discounting task and $\alpha 4\beta 2^*$ nAChR density levels in both the ventral (A) and dorsal (B) hippocampus.

Figure 5.

Scatter plots and regression lines showing relationships ($p < .05$) between rats' percent choice of the large reward in the discounting tasks and $\alpha 4\beta 2^*$ nAChR binding density in prefrontal cortical subregions. An inverse relationship was found between preference for the large delayed reward in the delay discounting task and $\alpha 4\beta 2^*$ nAChR density levels in both the orbitofrontal (A) and medial prefrontal (B) cortex, as well as between the large risky reward in the probability discounting task and $\alpha 4\beta 2^*$ nAChR density levels in the medial prefrontal cortex (C).

Figure 6.

Scatter plots and regression lines showing relationships ($p < .05$) between rats' percent choice of the large reward in the discounting tasks and $\alpha 4\beta 2^*$ nAChR binding density in nucleus accumbens subregions. An inverse relationship was found between preference for the large delayed reward in the delay discounting task and $\alpha 4\beta 2^*$ nAChR density levels in both the nucleus accumbens core (A) and shell (B), as well as between the large risky reward in the probability discounting task and $\alpha 4\beta 2^*$ nAChR density levels in the nucleus accumbens shell (C).

Figure 7.

Scatter plots and regression lines showing relationships ($p < .05$) between rats' percent choice of the large reward in the delay discounting task and $\alpha 4\beta 2^*$ and $\alpha 7$ nAChR binding density levels in the basolateral amygdala. An inverse relationship was found between rats' percent choice of the large delayed reward and both $\alpha 4\beta 2^*$ (A) and $\alpha 7$ (B) nAChR density levels the basolateral amygdala.

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Table 1

Correlation matrix displaying linear relationships between nAChR density levels and performance in decision making tasks.

	OFC	mPFC	CC	AIC	vHipp	dHipp	dSTR	NAcC	NAcS	BLA	VTA
$\alpha 4\beta 2$											
% choice of											
large risky	$r = -.38$	$r = -.58$	$r = -.30$	$r = -.49$	$r = -.44$	$r = -.16$	$r = -.25$	$r = -.37$	$r = -.61$	$r = -.11$	$r = .18$
reward	$p = .18$	$p = .031^*$	$p = .29$	$p = .08$	$p = .11$	$p = .59$	$p = .39$	$p = .22$	$p = .028^*$	$p = .76$	$p = .57$
% choice of											
large delayed	$r = -.56$	$r = -.56$	$r = .19$	$r = -.48$	$r = -.83$	$r = -.87$	$r = -.52$	$r = -.73$	$r = -.64$	$r = -.61$	$r = -.24$
reward	$p = .039^*$	$p = .036^*$	$p = .49$	$p = .09$	$p < .001^+$	$p < .001^+$	$p = .06$	$p = .004^*$	$p = .018^*$	$p = .045^*$	$p = .43$
$\alpha 7$											
% choice of											
large risky	$r = .37$	$r = .18$	$r = .25$	$r = .26$	$r = -.06$	$r = -.06$	$r = .13$	$r = .16$	$r = -.32$	$r = -.41$	$r = -.12$
reward	$p = .18$	$p = .50$	$p = .37$	$p = .35$	$p = .82$	$p = .83$	$p = .64$	$p = .67$	$p = .25$	$p = .13$	$p = .68$
% choice of											
large delayed	$r = -.38$	$r = -.36$	$r = .11$	$r = .25$	$r = -.03$	$r = -.22$	$r = -.07$	$r = .31$	$r = -.28$	$r = -.54$	$r = -.05$
reward	$p = .16$	$p = .19$	$p = .69$	$p = .37$	$p = .90$	$p = .42$	$p = .80$	$p = .39$	$p = .31$	$p = .039^*$	$p = .85$

⁺ = significant with Bonferroni correction ($p < .001$)* = significant without Bonferroni correction ($p < .05$)