



Acute effects of nicotine administration during prospective memory, an event related fMRI study

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ARTICLE INFO

Article history:

Received 2 August 2010

Received in revised form 17 February 2011

Accepted 11 April 2011

Available online 16 April 2011

Keywords:

Prospective memory

BA10

Nicotine

Acute psychopharmacology

ABSTRACT

We previously demonstrated that stimulating neuronal nicotinic acetylcholine receptors modulates prospective memory (PM), the ability to remember and implement a prior intention. Here we used fMRI to explore the neuronal correlates of acute nicotinic (1 mg) modulation during PM, employing a double blind, valence-matched placebo-controlled design, and a solely event-related analysis. Eight healthy adults completed on two occasions (1 week washout) a simple attentional task containing infrequent PM trials. PM activated bilateral parietal, prefrontal (BA10) and anterior cingulate, and deactivated general cingulate and medial prefrontal regions. Further, acute nicotine administration decreased activity within a largely overlapping right parietal region. This data validates a purely event-related approach to exploring PM, and suggests procholinergic modulation of PM by parietal rather than BA10/frontal regions.

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1. Introduction

Prospective Memory (PM) is the memory associated with a plan or intention to undertake an act or action at some later date (Ellis, 1996). The successful implementation of these intentions may be delayed by minutes, hours or days from the point of encoding, nevertheless PM is an important cognitive feature in successfully managing everyday life, e.g. remembering to buy a card for a friend's birthday or to meet a colleague for lunch, rely on implementing delayed intentions. As we get older however, PM failures are a persistent feature of memory decline (Einstein & McDaniel, 1990; Henry, MacLeod, Phillips, & Crawford, 2004; Kliegel, Jager, & Phillips, 2008; Maylor & Logie, 2010), and pharmacological facilitation of PM may therefore have significant application in sustaining functional independence in older adults. To this end, understanding both the neuroanatomical structures that support PM and the routes by which neurochemical systems modulate them is necessary.

Three decades of studies have detailed the significant role for the cholinergic neurotransmitter system in modulating memory and attention (for overviews see Heishman, Kleykamp, & Singleton, 2010; Levin, McClernon, & Rezvani, 2006; Robbins &

Roberts, 2007). Most compounds that are licensed for use with older adults are symptomatic treatments that sustain activity within the cholinergic neurotransmitter system, and for which there is evidence of some broad cognitive benefit (Cummings, Mackell, & Kaufer, 2008). Consistent with these findings, there is a body of literature indicating cognitive benefits from the stimulation of neuronal nicotinic receptors within the cholinergic neurotransmitter system in older adults with dementia (Newhouse, Potter, Kelton, & Corwin, 2001), older adults with mild cognitive impairment (Dunbar & Kuchibhatla, 2006) and with young healthy adults (Heishman et al., 2010). While under certain conditions, PM may be achieved via automatic processes (Einstein & McDaniel, 2005; McDaniel & Einstein, 2000; McDaniel, Guynn, Einstein, & Breneiser, 2004), many behavioural studies indicate PM engages attention-demanding processes, as evidenced by a 'cost' to holding an intention in mind; i.e., reduced accuracy or increased reaction time during an ongoing task may be observed when also holding an additional intention in mind (Marsh, Hicks, & Cook, 2005; R.E. Smith, 2003; R.E. Smith & Bayen, 2004). If attention is engaged by PM, then pharmacological compounds that affect attention should influence PM performance. Recent studies have reported that nicotine, a cholinergic agonist at neuronal nicotinic receptors improves PM (Marchant, Trawley, & Rusted, 2008; Rusted, Sawyer, Jones, Trawley, & Marchant, 2009; Rusted & Trawley, 2006; Rusted, Trawley, Heath, Kettle, & Walker, 2005). A question remains, however, as to how this modulation is achieved.

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Reviewing the functional neuroimaging literature investigating PM reveals important contributions from the prefrontal cortex, with activity within rostral BA10 being reported frequently (Burgess, Quayle, & Frith, 2001; Burgess, Scott, & Frith, 2003; Ouden, Frith, Frith, & Blakemore, 2005; Okuda et al., 1998, 2007; Simons, Owen, Fletcher, & Burgess, 2005; Simons, Scholvinck, Gilbert, Frith, & Burgess, 2006). Further, patients with lesions within BA 9/10 also display deficits in PM ability (Burgess, Veitch, de Lacy Costello, & Shallice, 2000). Drawing on findings of lesion studies conducted since the 1930s, Burgess, Gilbert, and Dumontheil (2007) demonstrate the importance of rostral BA10 to prospective memory processes in multiple contexts, and together with other meta-analyses, reveal functional differentiation within these regions, contrasting stimulus oriented memory and retrieval processing within lateral regions with stimulus invariant or internally oriented processing within medial regions of rostral BA10 (Burgess et al., 2007; Gilbert et al., 2006). BA10 activation may not define the locus of the procholinergic effects on PM performance, however. Nicotinic stimulation improves PM accuracy without altering the index of overt attention/working memory associated with a PM task, namely the RT/accuracy 'cost' of carrying an intention (Rusted & Alvares, 2008; Rusted et al., 2005). Also, there is increasing consensus that procholinergic effects on cognitive performance are less robust for classic measures of frontal executive function such as the Stroop task, or task-switching (Heishman et al., 2010). It is recognised that executive memory processes which underlie PM are also importantly shaped by wider activity with a frontoparietal network.

Recent meta-analyses drawing on large numbers of published functional activation maps clearly illustrate fronto-parietal networks where activity within both regions are correlated (S.M. Smith et al., 2009), networks whose function is relevant to attentional, working memory, episodic retrieval and conscious perception processes (Naghavi & Nyberg, 2005). This is supported by increasing understanding of how the parietal cortex, and in particular the inferior parietal lobe (Brodmann area 40) contribute to attentional tasks, maintaining representations of a number of potential responses (Bunge, Hazeltine, Scanlon, Rosen, & Gabrieli, 2002), processing stimulus salience and allocating attention to task-relevant information (Bisley & Goldberg, 2010; Corbetta & Shulman, 2002; Rossi, Pessoa, Desimone, & Ungerleider, 2009). Importantly, neuroimaging research into PM performance also demonstrates an important parietal contribution, most frequently observed within BA40 (Burgess et al., 2001; den Ouden, Frith, Frith, & Blakemore, 2005; Gilbert, Gollwitzer, Cohen, Burgess, & Oettingen, 2009; Martin et al., 2007; Simons et al., 2006), often together with activity within prefrontal regions. Further evidence is provided by Simons et al. who compared 2 PM conditions; a cue identification PM condition where the cue was made more or less salient, and an intention retrieval PM condition where the amount of action necessary to identify a PM target was varied. Both prefrontal and parietal activity was observed in each condition (Simons et al., 2006) suggesting a consistently relevant contribution from fronto-parietal networks in mediating PM. Taken together, these findings suggest that nicotinic stimulation may influence PM performance, and that this may occur via neuro-modulation within parietal regions.

The PM task we used in this study has been demonstrated previously to be an effective measure of PM, and to be sensitive to modulation by the cholinergic agonist nicotine (Marchant, King, Tabet, & Rusted, 2010; Rusted et al., 2009). It is used here as it delivers the requirements of a PM task in a format conducive to event-related recording in the scanner. Burgess et al. summarise the defining characteristics of a PM task as follows: there is a delay interval between forming an intention and carrying it out; there is an attention-demanding ongoing task and a PM task that involve distinct processing requirements (unlike a vigilance task,

where the two are not separate or distinct); the PM action is self-initiated – the ongoing task performance should not halt or change at the point where the intention should be carried out, unless the performer recognises the retrieval cue or context and initiates interruption of the ongoing task (Burgess et al., 2001). In practice, the PM component is usually a cue item that repeats infrequently within the ongoing task sequence, and for which a distinct response is required. While an analogous repeat of a predefined target typically is present only in certain everyday situations (e.g. taking medication after lunch each day), it is a standard in lab-based PM paradigms. Loft, Kearney, and Remington (2008) demonstrated in practice that repetition over blocks did not alter the nature of the PM response; Reynolds, West, and Braver (2009) also have demonstrated that this response is neurally distinct from a response to an infrequently repeated item that is not part of the PM task. Based on these findings, we explored the influence of acute nicotinic modulation during an entirely event-related PM task within a circumscribed network of neural regions demonstrated to be relevant to PM processes, and hypothesised that (1) PM would activate prefrontal (BA10) and parietal regions, and (2) that acute nicotinic receptor stimulation will influence performance by altering neural activity in parietal regions associated with engaging attention to the task, but will not alter neural activity in frontal BA 10 regions associated with PM.

2. Materials and methods

2.1. Participants

Eight right-hand dominant non-smoking volunteers were recruited at the University of Sussex, 6 females and 2 males, ranging between 19 and 30 years old (M: 23.4 years, SD: 3.8). Exclusion criteria comprised BMI outside normal range; high blood pressure or heart problems; any psychiatric or neurological illness or medication (including psychotropics and use of inhalers but excluding the contraceptive pill); pregnancy or breastfeeding; metallic implants, pacemakers, tattoos or braces. All participants volunteered under a written informed consent procedure approved by University of Sussex School of Life Sciences Ethics Committee.

2.2. Nicotine delivery

Nasal sprays comprised individual bottles with mechanical spray pumps that delivered 0.5 mg of nicotine or a matched inactive placebo per spray. In a double-blind procedure, nasal sprays were coded by an independent third party and each volunteer was allocated to receive nicotine in one session and placebo in the other. For each session, volunteers self-administered 2 puffs from the allocated spray, one in each nostril, delivering 1.0 mg nicotine or matched placebo. This dose tends to be at the low end of the range of doses associated with cognitive effects (see Heishman et al., 2010); previous studies have reported reliable cognitive effects (Marchant et al., 2010; Rusted et al., 2009), significantly, these occur without associated subjective effects. Peak plasma levels are reached 15 min after delivery (Schneider, Lunell, Olmstead, & Fagerstrom, 1996). Nasal sprays were provided by AB McNeil, Helsingborg, Sweden.

2.3. Design

Participants attended 3 sessions: in the first session (2–5 days before the first scanning session), volunteers practised the ongoing card sort task, and practised self-administration with a placebo nasal spray. Equal numbers of volunteers (four) received nicotine or placebo in the first session, and the alternative treatment in the second session. In each of the scanning sessions, volunteers received a short practice run with the ongoing card sort task and the additional PM instruction (see below). Nasal sprays then were self-administered and fMRI scanning commenced 18–20 min later. The two session within-subject manipulation used here is essential to the pharmacological/neuroimaging component of this study, which cannot be completed in a single session. It is a departure from a standard PM paradigm that traditionally exposes the volunteer to only one PM session – the justification being that in the second session the participants are not naïve to the PM instructions in the way that they are in the first. We had previously piloted the PM task used here under repeat session conditions: data demonstrated that while the sort RTs were non-significantly faster in the second session, there remained a significant intention effect (sort trials in the PM condition were 60–80 ms slower on average than baseline sort-only trials); in addition, PM accuracy improved but remained substantially below ceiling. Thus we were confident that the PM effect was sustained across sessions, despite lack of naïvety.

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