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Systematic review: Effects of cholinergic signaling on cognition in human pharmacological studies

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ABSTRACT

Acetylcholine (ACh) is one of the main neurotransmitters in central nervous systems across species. It has been extensively studied in animal models, and is known for its profound role in attention processes and adaptive responses to changing environments. Recent theories propose that this occurs by modulating the relative influence of top-down and bottom-up inputs during perceptual inference and regulating cue-validity updating in uncertain environments. However, the role of ACh in human cognition has mostly been investigated in memory and is less well established in other domains. Here we provide a systematic review of human studies investigating effects of ACh on cognitive functions using pharmacological modulators, with a focus on the cognitive processes needed for acute behavioural adaptation to situational changes. Results revealed that ACh is involved in sustained attention, perceptual detection, the updating of cue-response relationships and the speed of information processing, with differential cognitive effects associated with muscarinic and nicotinic modulators. This supports a role of ACh in prioritizing top-down and bottom-up information in humans, potentially enabling rapid updating of behavioural responses to situational changes. However, efforts to parse out the molecular roles of ACh signaling with pharmacological methodologies may be limited by their relative nonspecificity and an inability to mimic signaling dynamics. Integration of pharmacological findings with neuroimaging data such as functional magnetic resonance spectroscopy may be helpful to identify the effects of cholinergic modulators on whole-brain pharmacodynamics.

1. Introduction

Acetylcholine (ACh) is an important neuromodulator involved in many cognitive functions. In humans, cholinergic signaling has been studied mostly in relation to memory deficits such as in Alzheimer's disease (Chen et al., 2022; Qian et al., 2022). However, in animal studies, cholinergic function has been implicated in many cognitive processes relevant for adaptive responding under stress, such as in a rapidly changing environment filled with uncertainty. Recently, there has been growing interest in the role of ACh in perceptual precision and belief adaptation, relevant for adaptive responding in animals under threat (Mikulovic et al., 2018; Mineur and Picciotto, 2021). Whether ACh has a similar role in human congition is less clear. This literature review provides a systematic overview of human studies on the effects of ACh pharmacological modulators on cognitive function, with a particular focus on the short-term, "online" cognitive processes that are directly relevant to decision-making and to the acute, situational adaptation of human behaviour.

Acetylcholine is produced in the basal forebrain, the midbrain (i.e. pedunculoptine nucleus (PPN) and laterodorsal tegmental nucleus) and striatal interneurons. In all systems, ACh acts as a neuromodulator, altering presynaptic release of other neurotransmitters and influencing responses of entire networks of neurons (Bentley et al., 2011; Mena-Segovia and Bolam, 2017; Picciotto et al., 2012; Yu and Dayan, 2002). ACh from the basal forebrain upregulates feed-forward cortical inputs from the thalamus, and at the same time suppresses intracortical

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feed-back connections (Hasselmo and Giocomo, 2006). High levels of ACh within the basal forebrain pathway thus can reduce processing of previously-formed top-down inputs to effectively facilitate bottom-up sensory input processing (Hasselmo and McGaughy, 2004), supporting learning and adaptation to uncertainty. Accordingly, ACh has been shown to be involved in processes of memory encoding, recall, learning and attention (Atri et al., 2004; Hasselmo, 2006; Klinkenberg et al., 2011). Animal studies modulating ACh levels using brain lesions or administration of cholinergic antagonists have further shown worse performance on tests of sustained and divided attention, impairments in episodic memory encoding tasks, and also reduction in the acquisition of conditioned fear (Hasselmo and Giocomo, 2006; Hasselmo and Sarter, 2011; McGaughy et al., 1999; Newman and McGaughy, 2008; Wilson and Fadel, 2017). In humans, research has largely focused on the role of cholinergic signaling in memory dysregulation, manifesting in disorders such as Alzheimer's disease (Chen et al., 2022; Qian et al., 2022), which is characterized by a failure to encode and store new memories.

At the same time, ACh is also a key player in the autonomic nervous system (ANS). ACh is released by all preganglionic cells in the ANS and by the postganglionic cells in parasympathetic fibers, thereby serving as the primary excitatory neurotransmitter of the parasympathetic branch. Important interactions exist between central and peripheral ACh signalling. Coordination of both can be achieved through cholinergic signaling between cholinergic nuclei such as the nucleus ambiguus (NAm) or the dorsal motor nucleus of the vagus (DMV) and the PPN (Bertrand and Wallace, 2020). This is supported by single-neuron tracing studies showing that the descending collaterals of cholinergic PPN neurons arise from neurons that also have ascending projections (Mena-Segovia et al., 2008; Zhao et al., 2023). Specifically, the NAm and DMV contain preganglionic parasympathetic neurons synapsing on various target organs such as the heart or the lungs, thus mediating parasympathetic-related behaviours such as bradycardia (Hsieh et al., 1998; Wang et al., 2001). Therefore, ACh signaling in the CNS can not only control cognitive functions directly by ascending projection to other brain structures, they are also able to indirectly regulate ANS behaviours via descending projection and determine whether the body is in a more action or perception-focused state. This is crucial in behaviours that involve both the cognitive and somatic systems and require strict coordination between them.

One notable example of behaviour requiring integration of ANS and CNS activation is threat-anticipatory freezing, associated in the literature with ACh signaling (Kellis et al., 2020; Nail-Boucherie et al., 2000; for a review, see Roelofs and Dayan, 2022). This behaviour is part of the well-described defensive freeze-fight-flight cascade, occurring if the animal has perceived threat in its environment but judges it not to be immediate (Roelofs, 2017; Rösler and Gamer, 2019). Parasympathetic dominance over the sympathetic ANS branch during freezing has been linked to bradycardia and immobility, which has in turn been associated with improved perceptual sensitivity, increased value integration during decision making, and enhanced action preparation (de Voogd et al., 2022; Henderson et al., 2024; Klaassen et al., 2021; Lojowska et al., 2015). This thus raises the question whether upregulation of these functions in the CNS is linked to cholinergic function as well. Freezing typically occurs in instances of 'expected uncertainty', where a conditioned cue signals threat but there is unreliability in the predictive relationship (Roelofs and Dayan, 2022; Yu and Dayan, 2005). In support of a cholinergic role in freezing, animal studies have robustly shown ACh involvement in signaling expected uncertainty by linking cholinergic signaling to precision (i.e. inverse uncertainty) of probability prediction errors (PE), regulating the prioritization of bottom-up sensory information over top-down expectations and thus the speed of updating cue validity beliefs (Crouse et al., 2020; Krawczyk et al., 2021; Pérez-González et al., 2024; Yu and Dayan, 2002). Increasing focus has been dedicated to investigating a similar function of ACh in humans: for example, cholinergic signaling in the PPN has been shown to represent mismatches between expected and actual outcomes, enabling context-sensitive shifts in arousal states (Mena-Segovia and Bolam, 2017). Iglesias et al. (2013) also found that ACh levels may signal precision of high-level PEs and thus influence the rate of changes in cue-outcome contingency estimates. Nevertheless, works studying these relations are still relatively scarce, and neither has there been a systematic overview of related evidence in humans. Thus, there is a considerable gap in knowledge on the role of cholinergic signaling in humans.

The present review aims to provide a systematic overview of human studies investigating the effects of ACh pharmacological modulators on cognitive function. Specifically, the role of ACh in cognitive functions relevant for direct and immediate updating of behavioural responses to situational changes, such as acute threat, will be presented. These are categorized into six broad processes: attention, perceptual sensitivity, belief adaptation, information processing, action preparation and behaviour inhibition (see Table 1). The 'attention' category includes sustained attention, selective attention or attentional allocation tasks, while 'perceptual sensitivity' encompasses perceptual detection as well as discrimination threshold tasks. Both are relevant to the bottom-up processing of sensory information for perceptual judgements. 'Belief adaptation' in this paper is defined as speed of sensory belief updating based on environment predictability and covers learning rate tasks measuring the ability of participants to acquire novel predictive relationships (e.g. PE signaling). 'Information processing' involves tasks measuring speed of mental manipulation of information (eg. spatial rotation tasks), relevant to the speed of situational cue processing. 'Behaviour inhibition' covers tasks measuring the extent of inhibition of a default behaviour (eg. stop signal task), while 'action preparation' addresses speed of motor executionsuch as finger tapping, and these processes are involved in the execution of the adapted behaviour. Of note, memory studies that go beyond PE based updating are outside the scope of this review as they have been well-reviewed elsewhere (Huang et al., 2022), and because its link to immediate behavioural adaptation is not as strong. This excludes more explicit memory types of tasks, such as recognition retrieval and consolidation studies, where the role of ACh have been well-established.

2. Methods

2.1. Search strategy

This review was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. An electronic search was conducted on the PubMed, EMBASE and PsycInfo databases on 13 June 2023. A search string was designed based on eligibility criteria discussed in the following section, used on all databases and is as follows: ("acetylcholine" AND ("agonist" OR "antagonist" OR "pharmacological")) AND ("visual perception" OR "auditory perception" OR "sensory processing" OR "perception" OR "attention" OR "planning" OR "decision making" OR "risk assessment" OR "action preparation" OR "behavioural inhibition" OR "behavioral inhibition" OR "expected unpredictability" OR "expected uncertainty" OR "cognitive control" OR "uncertainty" OR "belief adaptation" OR "aversive processing" OR "attentional resource allocation" OR "associability" OR "perceptual inference" OR "attentional effort") AND ("human" OR "humans" OR "subjects") NOT ("rats" OR "rat" OR "mice" OR "bees" OR "zebrafish") NOT review.

All studies were exported and duplicates removed in Endnote X9. Manual title screening was conducted, followed by abstract screening if the title did not fulfil any exclusion criteria. Finally, full text analysis for all potential studies was conducted to ensure eligibility for inclusion in the final analysis. Reference lists of selected articles were further looked through to expand the retrieval search for relevant papers.

Table 1
Operationalisation of cognitive processes and examples of tasks included.

Cognitive process	Operationalisation	Examples of tasks included
Attention	Sustained attention	Adaptive tracking test (Alvarez-Jimenez et al., 2018; Baakman et al., 2017; Bakker et al., 2021) Continuous performance task (Barr et al., 2008; D'Souza et al. 2012; Ettinger et al., 2017; Roh et al., 2014; Veselinović et al., 2015) Sustained attention to response task (Borghans et al., 2020; Smucny et al., 2016) Rapid visual information processing task (Bakker et al., 2021; Ellis et al., 2006; Hahn et al., 2020; Knott et al., 2011, 2012; Yuille et al., 2017) Attention network task (Ettinger et al., 2017; Thienel et al., 2009; Veselinović et al., 2015; Wignall and de Wit, 2011)
	Selective attention	Simon task (Danielmeier et al., 2015; Ettinger et al., 2017) Dichotic listening test (Drachman et al., 1980; Dunne and Hartley, 1985) Attention network task (Ettinger et al., 2017; Thienel et al., 2009; Veselinović et al., 2015, Wignall and de Wit, 2011)
	Attention allocation	Matching task (Bentley et al., 2003; Furey et al., 2008) Cued-visual search task/ visual cueing paradigm (Breckel et al., 2015; Levy et al., 2000) Attention network task (Ettinger et al., 2017; Thienel et al., 2009;Veselinović et al., 2015, Wignall and de Wit, 2011)
Perceptual sensitivity	Perceptual detection	Simple reaction time test (Alvarez-Jimenez et al., 2018; Baakman et al., 2017; Borghans et al., 2020; Brown et al., 2015; Ellis et al., 2006; Jepma et al., 2018; Knott, Choueiry, et al., 2014; Little et al., 1998; Pham et al., 2020) Novelty oddball task (Bakker et al., 2021; Caldenhove et al., 2017; Choueiry et al., 2020; Harkrider and Hedrick, 2005; Klinkenberg et al., 2013; Knott et al., 2012; Knott, Choueiry, et al., 2014; Knott, Impey, et al., 2014; Nathan et al., 2022; Pekkonen et al., 2005; V. Knott, D. Impey et al., 2015) Critical flicker fusion (Ellis et al., 2006; Erskine et al., 2004)
	Discrimination thresholds	Spatial discrimination threshold test (Bliem et al., 2008) Auditory discrimination task (Cohen et al., 1994) Contrast determination task (Boucart et al., 2015) IT task (Erskine et al., 2004; Thompson et al., 2000)
Belief adaptation	Speed of associative belief updating	Repeated acquisition test (Newhouse et al., 1992, 1994) Stimulus-stimulus learning task (Iglesias et al., 2021) Cue-target detection task (Thiel et al., 2005; Thiel and Fink, 2008)
Information processing	Speed of mental information manipulation	Trail making test (Veselinović et al., 2015; Voss et al., 2010) Tower of London (Voss et al., 2010)
Behaviour inhibition	Speed of inhibition of default behaviour	Stroop task (Baakman et al., 2017; Barr et al., 2008; D'Souza et al. 2012; Ettinger et al., 2017; Roh et al., 2014; Wignall and de Wit, 2011) Body sway (Bakker et al., 2021; Baakman et al., 2017) Choice reaction time task (D'Souza et al. 2012; Ellis et al., 2006; Ettinger et al., 2017; Laube et al., 2017; Newhouse et al., 1992, 1994; Potter et al., 2012) Stop signal task (Kasparbauer et al., 2019; Potter et al., 2012; Wignall and de Wit, 2011)
Action preparation	Speed of motor execution	Finger tapping (Alvarez-Jimenez et al., 2018; Bakker et al., 2021; Baakman et al., 2017; D'Souza et al. 2012)

2.2. Eligibility criteria

Studies were selected if they fulfilled all the following eligibility criteria: (1) studies pharmacologically manipulating extent of cholinergic transmission, (2) studies reporting objective data on the aforementioned cognitive domains, (3) randomized controlled trials or studies comparing effects of treatment groups with control groups using placebo, and finally (4) studies in healthy human participants.

Exclusion criteria are as follows: (1) case studies, review articles or conference abstracts, (2) studies that did not report selected outcomes, (3) studies without manipulation of acetylcholine level, (4) studies conducted in a non-healthy population and (4) animal studies.

No limitations on date were implemented in order to capture the broadest and thus most accurate picture of the current research landscape on ACh effects on cognition.

2.3. Data extraction

Data extraction and categorisation into the six cognitive domains was conducted by one reviewer, and then checked by a second reviewer. Discrepancies were resolved through discussion. Extracted data were pre-defined into two sets, demographic data and outcome data. Demographic data included the number of participants, gender breakdown, age breakdown, drug used, dosage administered, and type of administration (eg. transdermal, intravenous). Outcome data included the drug category (eg. nicotinic, muscarinic or general, agonist or antagonist), the measured cognitive domain, the specific task examined, the result of the task based on the study's statistical analyses, recorded peripheral side effects and performance moderators, if any were studied.

2.4. Risk of bias

The quality of the 84 studies were assessed using ROB2, the Cochrane risk-of-bias assessment tool. The versions for crossover trials and parallel-group trials were used. Risk of bias assessments were conducted by two independent reviewers.

3. Results

3.1. Summary of studies

A total of 451 records were identified. 305 records remained after duplicate removal and were screened by title and abstract. 93 records remained for full text assessment, leaving 52 studies for inclusion in the review. Manually searching through the references of these 52 articles resulted in the additional identification of 32 studies. These were

similarly screened by title, abstract and full-text assessment and all were included in final analysis, bringing the total number of eligible studies to 84. The study flowchart is shown in Fig. 1.

3.2. Characteristics of included studies

A total of 2194 participants were included in this review, of which 1299 were male. Gender breakdown statistics were not reported in four studies (Becker et al., 2013; Bunzeck et al., 2014; Drachman et al., 1980; Nathan et al., 2001). 11 studies were randomized controlled trials, while the remaining 72 were randomized crossover trials. Demographic data of the 83 included studies as well as outcome data are presented in Supplementary tables 1 and 2 respectively, arranged by drug category and cognitive domain.

Effects of nicotinic agonists were the most well characterized with 31 studies, followed by muscarinic antagonists administered by 24 studies. 15 studies investigated the effect of general agonists, while 11 studies examined the effect of nicotinic antagonists. The last four studies administered muscarinic agonists. Drugs were most commonly administered orally, intravenously or transdermally, though the latter was almost exclusively done when administering the nicotinic agonist nicotine. Less popular were subcutaneous injection (Boucart et al., 2015; Drachman et al., 1980), and intramuscular injection (Ellis et al., 2006; Erskine et al., 2004), which were performed in only two studies each. Another two studies did not report method of drug administration (Nathan et al., 2001, 2022).

Broadly, a total of 13 different cholinergic modulators across all drug categories were tested. Details of the specific pharmacological modulators used will be discussed in each separate drug category subsection, organized by receptor subtype.

3.3. Results of risk of bias assessment

The results of the ROB2 assessment can be found in Table 2, for randomized parallel studies, and Table 3 for randomized crossover trials. The evidence base was largely moderate in methodological quality, though notably, only two studies (Nathan et al., 2022; Petrovsky et al., 2012) published pre-established protocols. A number of crossover studies also did not randomize or counterbalance for treatment order.

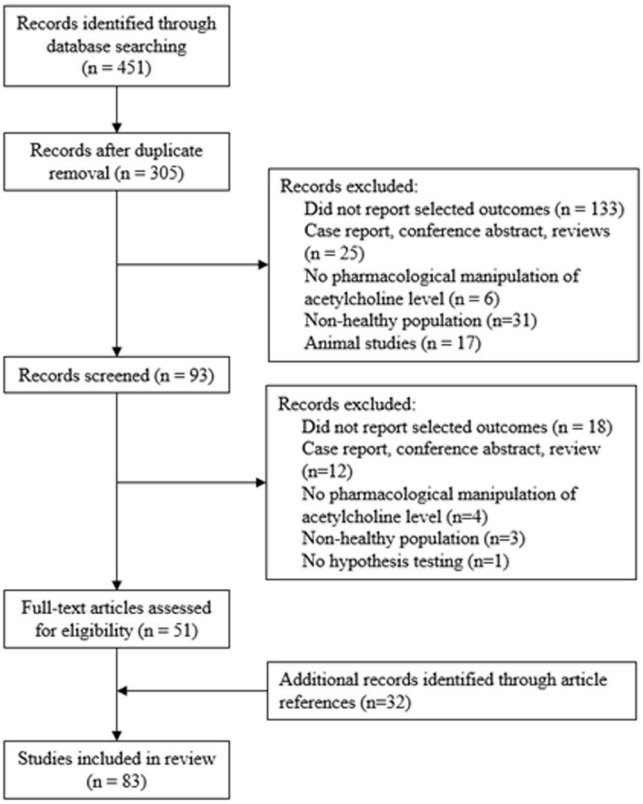

Fig. 1. PRISMA Flowchart.

3.3.1. Muscarinic antagonists

The two main muscarinic antagonists studied were scopolamine and biperiden. A high-affinity, non-specific antagonist, scopolamine has been previously prescribed for nausea and motion sickness. In this review, the range of scopolamine dosage began from 0.2 mg up to 1.5 mg, with a mode of 0.4 mg. Biperiden is a M1/M4-specific anticholinergic regularly used to treat Parkinsonism, and was dosed from 2 mg – 6 mg in this review. Most studies administered a flat dosage to all participants, but Danielmeier et al. (2015) administered biperiden at a weight-dependent dose of 0.04 mg/kg, while Furey et al. (2008) administered scopolamine at 0.04 μg/kg.

3.3.1.1. Attention. Overall, 11 studies assessed the effect of muscarinic antagonists on attention, of which four studied sustained attention and three studied selective attention. Conflicting evidence was found for the role of muscarinic antagonists on attention as a whole. No significant differences were found between studies administering biperiden or scopolamine.

Five studies found reductions in attention performance (Baakman et al., 2017; Bakker, van Esdonk, et al., 2021; Danielmeier et al., 2015; Drachman et al., 1980; Furey et al., 2008), while no effect was found in three studies (Borghans et al., 2020; Dunne and Hartley, 1985; Levy et al., 2000). Conflicting results were found in the remaining three studies with implementation of multiple attention tasks. Veselinović et al. (2015) found no effect of biperiden on alerting, orienting and executive attention with the attention network test but an impairment of sustained attention with a continuous performance task, while Ellis et al. (2006) observed sustained attention, and found impairments on the digit vigilance task, but not the rapid visual information processing task. Renate Thienel et al. (2009) found no effect of scopolamine on alerting and orienting attention, but saw a significant change in executive attention performance.

Split by attention subtype, the strongest evidence was provided for a role of muscarinic receptors in sustained attention, with four of six tasks reporting significant effects of biperiden or scopolamine (Baakman et al., 2017; Bakker, van Esdonk, et al., 2021; Ellis et al., 2006; Veselinović et al., 2015). Evidence for selective attention tended towards no role of muscarinic antagonists, with two of three studies observing no significant effect (Drachman et al., 1980; Dunne and Hartley, 1985; Levy et al., 2000). The effect of muscarinic antagonists on alerting or orienting attention processes is not supported by this review (Renate Thienel et al., 2009; Veselinović et al., 2015), whereas evidence points towards an effect on attentional control, with significant reductions in attention found by three of four studies (Danielmeier et al., 2015; Furey et al., 2008; Renate Thienel et al., 2009).

3.3.1.2. Perceptual sensitivity. Changes in perceptual sensitivity were observed by 18 studies utilising tasks examining perceptual detection abilities, sensory discrimination thresholds as well as preattentive sensory change detection. Evidence supported a role of muscarinic receptors in perceptual enhancement, but discrimination sensitivity and preattentive change detection processes were not affected. Possible differences in the cognitive impact of muscarinic receptor subtypes were identified.

Of the 11 studies specifically examining the influence of muscarinic antagonists on perceptual detection, eight saw significant reductions in performance or speed (Baakman et al., 2017; Brown et al., 2015; Ellis et al., 2006; Erskine et al., 2004; Jepma et al., 2018; Little et al., 1998; Robbins et al., 1997; Renate Thienel et al., 2009). The remaining three

Table 2
Cochrane Risk of Bias Assessment Tool for Randomized Parallel Studies.

	Randomization sequence generation	Deviation from intended intervention	Incomplete data	Measurement bias	Selective reporting	Overall bias
Becker et al. (2013)	Low	Low	Low	Low	Some concerns	Low
Bunzeck et al. (2014)	Some concerns	Low	Low	Low	Some concerns	Low
Chamoun et al. (2017)	Low	Low	Low	Low	Some concerns	Low
Iglesias et al. (2021)	Low	Low	Low	Low	Some concerns	Low
Marshall et al. (2016)	Low	Low	Low	Low	Some concerns	Low
Thiel et al. (2002)	Low	Low	Low	Low	Some concerns	Low
Thiel et al. (2002)	Low	Low	Low	Low	Some concerns	Low
Vossel et al. (2008)	Low	Low	Low	Low	Some concerns	Low
Nathan et al. (2022)	Low	Low	Low	Low	Low	Low
Cohen et al. (1994)	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Bentley et al. (2003)	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns

studies found no effect (Borghans et al., 2020; Levy et al., 2000; Veselinović et al., 2015), which may be attributed to differential effects of muscarinic receptor subtypes: two of the null finding studies utilised M1-specific antagonist biperiden instead of the general muscarinic agonist scopolamine, which was administered in the other perceptual detection studies. In terms of preattentive sensory change detection, three of four studies found no effect of muscarinic antagonist administration (Caldenhove et al., 2017; Klinkenberg et al., 2013; Pekkonen et al., 2005). Six of seven studies found no effect of scopolamine administration on discrimination sensitivity (Bliem et al., 2008; Boucart et al., 2015; Brown et al., 2015; Ellis et al., 2006; Erskine et al., 2004), with no studies examining the effect of biperiden administration. It may be notable that Cohen et al. (1994), the only discrimination sensitivity study which found an effect of scopolamine, utilised an auditory discrimination task that did not specifically probe the frequency discrimination threshold before and after scopolamine administration and is not considered sensitive in comparison to others, thus posing a risk of having spurious findings.

Interestingly, even while there was no effect on spatial discrimination, Bliem et al. (2008) found a reduction in learning effect with administration of scopolamine in a tactile discrimination threshold task. This effect may be linked to the well-documented inhibitive effect of muscarinic antagonists on belief adaptation, but may also imply an effect of muscarinic antagonists on perceptual learning.

3.3.1.3. Belief adaptation. Belief adaptation was robustly shown to be affected by muscarinic antagonists, independent of drug administered. Of the five studies investigating the effect of muscarinic antagonists on belief adaptation, four found a significant reduction in learning rate (Klinkenberg et al., 2012; Marshall et al., 2016; Thiel, Friston, et al., 2002; Thiel, Henson, et al., 2002), while only Iglesias et al. (2021) observed no effect. This suggests possible involvement of muscarinic receptors in belief updating.

In terms of adapting to changes in cue validity, conflicting evidence was found, but may be explained by dosage effects. Klinkenberg et al. (2012) found that the M1/M4-specific antagonist biperiden had no effect on learned irrelevance, a phenomenon where acquisition of association is delayed after prior non-contingent exposure to the conditioning stimuli, essentially suggesting that biperiden had no effect on the PE regulating estimates of cue-validity contingency. Conversely, Marshall et al. (2016) observed that biperiden administration reduced adaptability to changing associative probabilities. Further complicating the picture, Iglesias et al. (2021) observed biperiden-induced reductions in higher-level PEs in the cholinergic PPT, but also found enhancements in sensory PE. However, dosages of 2 mg and 4 mg administered respectively in Klinkenberg et al. (2012) and Iglesias et al. (2021) may have been insufficient to achieve physiologically required plasma levels of biperiden for signal modulation. This is in comparison to the 6 mg administered by Marshall et al. (2016), and may thus account for the observational discrepancies.

3.3.1.4. Information processing. Information processing tasks were investigated in three studies, where a role of muscarinic receptors in processing speed was not supported.

Two studies found no effect on processing speeds (Furey et al., 2008; Veselinović et al., 2015; Voss et al., 2010), and the last study found a reduction of processing speed (Veselinović et al., 2015). All studies administering scopolamine, which acts non-specifically, obtained null effects on processing, while the sole study administering the M1/M4 antagonist biperiden found a significant effect on processing speed. This may suggest receptor subtype differences, specifically pointing to a M1/M4-dependent role in processing speed.

3.3.1.5. Behaviour inhibition. Behavioural inhibition was measured by four studies (Baakman et al., 2017; Bakker, van Esdonk, et al., 2021; Ellis et al., 2006; Laube et al., 2017), and inconclusive results were obtained.

Two studies found a reduction in cognitive control with administration of muscarinic antagonists (Bakker, van Esdonk, et al., 2021; Ellis et al., 2006). Contrastingly, Laube et al. (2017) found no effect on behavioural inhibition with the choice reaction time task, while interestingly, Baakman et al. (2017) reported an increase in performance with scopolamine as measured by the Stroop task. Both discrepancies were not associated with drug dosage or task.

3.3.1.6. Action preparation. Only two studies looked at the effect of muscarinic antagonists on action preparation, precluding reliable conclusions. Though both studies measured action preparation with the finger tapping task, Bakker, van Esdonk, et al. (2021), which administered the M1/M4 antagonist biperiden, found no difference between conditions, while Baakman et al. (2017), which administered the general antagonist scopolamine, observed a reduction in the number of taps upon drug administration. Preliminarily, this may thus suggest a M1/M4-independent role of ACh on action preparation.

3.3.1.7. Peripheral side effects. Overall, five studies observed and reported side effects linked to the administration of muscarinic antagonists. Little et al. (1998), Brown et al. (2015); Jepma et al. (2018); Laube et al. (2017) studied the administration of scopolamine, and scopolamine was shown to reduce heart rate in all studies with the exception of Laube et al. (2017). This effect was inconsistently related to dosage, as Laube et al. (2017) administered 0.8 mg of scopolamine to no effect, whereas Little et al. (1998) found significant effects with a dosage of 0.4 mg. Brown et al. (2015) and Jepma et al. (2018) administered 1.2 mg and 1.6 mg of scopolamine respectively. Regarding the effect of scopolamine on blood pressure, all studies except Little et al. (1998)

Table 3
Cochrane Risk of Bias Assessment Tool for Randomized Crossover Studies.

	Randomization sequence generation	Period and carryover effects	Deviation from intended intervention	Incomplete data	Measurement bias	Selective reporting	Overall bias
Ahrens et al. (2015)	High	High	Low	Low	Low	Some concerns	Some concerns
Ahrens et al. (2020)	Low	Low	Low	High	Low	Some concerns	Some concerns
Alvarez-Jimenez et al. (2018)	Low	Low	Low	Some concerns	Low	Some concerns	Low
Baakman et al. (2017)	High	Low	Low	Low	Low	Some concerns	Some concerns
Bakker et al. (2021)	Low	Low	Low	Low	Low	Some concerns	Low
Bakker et al. (2021)	Low	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns
Barr et al. (2008)	Low	Low	Low	Low	Low	Some concerns	Low
Behler et al. (2015)	Low	Low	Low	Low	Low	Some concerns	Low
Bentley et al. (2004)	Low	Low	Low	Low	Low	Some concerns	Low
Bliem et al. (2008)	Low	Low	Low	Low	Low	Some concerns	Low
Borghans et al. (2020)	High	Low	Low	Low	Low	Some concerns	Some concerns
Boucart et al. (2015)	Low	Low	Low	Low	Low	Some concerns	Low
Breckel et al. (2015)	High	Low	Low	Low	Low	Some concerns	Some concerns
Brown et al. (2015)	Low	Low	Low	Low	Low	Some concerns	Low
Byrne et al. (2020)	Low	Low	Low	Low	Low	Some concerns	Low
Caldenhove et al. (2017)	Some concerns	Low	Low	Low	Low	Some concerns	Low
Choueiry et al. (2020)	Low	Low	Low	Low	Low	Some concerns	Low
Danielmeier et al. (2015)	Low	Low	Low	Low	Low	Some concerns	Low
Drachman et al. (1980)	High	Some concerns	Low	Low	Low	Some concerns	Some concerns
D'Souza et al. (2012))	Low	Some concerns	Low	Low	Low	Some concerns	Low
Dunne and Hartley (1985)	Low	Low	Low	Low	Low	Some concerns	Low
Ellis et al. (2006)	Low	Low	Low	Low	Low	Some concerns	Low
Erskine et al. (2004)	Low	Low	Low	Low	Low	Some concerns	Low
Ettinger et al. (2017)	Low	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Furey et al. (2008)	Low	Some concerns	Low	Low	Low	Some concerns	Low
Gratton et al. (2017)	Some concerns	Low	Low	Low	Low	Some concerns	Low
Hadjis et al. (2019)	Low	Some concerns	Low	Low	Low	Some concerns	Low
Hahn et al. (2020)	Low	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns
Harkrider and Hedrick (2005)	Low	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Impey et al. (2013)	Low	Some concerns	Low	Low	Low	Some concerns	Low
Jepma et al. (2018)	Low	Low	Low	Low	Low	Some concerns	Low
Kasparbauer et al. (2019)	Low	Low	Low	Low	Low	Some concerns	Low
Klinkenberg et al. (2012)	High	Low	Low	Low	Low	Some concerns	Some concerns
Klinkenberg et al. (2013)	Low	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns
Knott et al. (2009)	Low	Some concerns	Low	Low	Low	Some concerns	Low
Knott et al. (2011)	Low	Some concerns	Low	Low	Low	Some concerns	Low

(*continued on next page*)

Table 3 (*continued*)

	Randomization sequence generation	Period and carryover effects	Deviation from intended intervention	Incomplete data	Measurement bias	Selective reporting	Overall bias
Knott et al. (2012)	Low	Some concerns	Low	Low	Low	Some concerns	Low
Knott, Choueiry, et al. (2014)	Low	Some concerns	Low	Low	Low	Some concerns	Low
Knott, Impey, et al. (2014)	Low	Some concerns	Low	Low	Low	Some concerns	Low
Knott, de la Salle, et al. (2015)	Low	Low	Low	Low	Low	Some concerns	Low
Knott, Impey, et al. (2015)	Low	Low	Low	Low	Low	Some concerns	Low
Kosovicheva et al. (2012)	Low	Low	Low	Low	Low	Some concerns	Low
Laube et al. (2017)	High	Low	Low	Low	Low	Some concerns	Some concerns
Levy et al. (2000)	Some concerns	Some concerns	Low	Low	Low	Some concerns	Some concerns
Little et al. (1998)	Low	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns
Meyhöfer et al. (2019)	Low	Low	Low	Low	Low	Some concerns	Low
Moran et al. (2013)	Low	Low	Low	Low	Low	Some concerns	Low
Nathan et al. (2001)	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Nathan et al. (2013)	Low	Low	Low	Low	Low	Some concerns	Low
Newhouse et al. (1992)	Low	Some concerns	Low	Low	Low	Some concerns	Low
Newhouse et al. (1994)	Low	Some concerns	Low	Low	Low	Some concerns	Low
Pekkonen et al. (2005)	Low	Low	Low	Low	Low	Some concerns	Low
Petrovsky et al. (2012)	Low	Low	Some concerns	Some concerns	Low	High	Some concerns
Pham et al. (2020)	Low	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Potter et al. (2012)	Low	Some concerns	Low	Low	Low	Some concerns	Low
Robbins et al. (1997)	Low	Some concerns	Low	Low	Low	Some concerns	Low
Roh et al. (2014)	Low	Low	Low	Low	Low	Some concerns	Low
Rokem and Silver (2010)	Low	Low	Low	Low	Low	Some concerns	Low
Rokem et al. (2010)	Low	Low	Low	Low	Low	Some concerns	Low
Shah et al. (2011)	Low	Some concerns	Low	Low	Low	Some concerns	Low
Smucny et al. (2016)	Low	Low	Some concerns	Low	Low	Some concerns	Low
Sun et al. (2021)	Low	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns
Thiel and Fink (2008)	Low	Some concerns	Low	Low	Low	Some concerns	Low
Thiel et al. (2005)	Low	Low	Low	Low	Low	Some concerns	Low
Thienel et al. (2009)	Some concerns	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns
Thienel et al. (2009)	Some concerns	Low	Low	Low	Low	Some concerns	Low
Thompson et al. (2000)	High	Low	Low	Low	Low	Some concerns	Some concerns
Veselinović et al. (2015)	High	Low	Some concerns	Low	Low	Some concerns	Some concerns
Voss et al. (2010)	Low	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns
Vossel et al. (2014)	Some concerns	Low	Low	Some concerns	Low	Some concerns	Some concerns
Wignall and de Wit (2011)	Low	Some concerns	Low	Low	Low	Some concerns	Low
Yuille et al. (2017)	Low	Some concerns	Low	Low	Low	Some concerns	Low

reported that scopolamine did not affect blood pressure. The final study, Danielmeier et al. (2015), reported that biperiden decreased heart rate and systolic pressure.

3.3.2. Muscarinic agonists

Muscarinic agonists are linked to high occurrences of peripheral adverse effects and are not commonly used in clinical settings or for exploratory studies. To overcome this, researchers have turned to positive allosteric modulators of muscarinic agonists, which do not directly activate the muscarinic receptor but instead bind to an allosteric site to enhance the response to endogenous ACh (Moran et al., 2018). However, to our knowledge, no study has examined the effect of administration of PAMs in human participants. It may be interesting to note that KarXT, a drug comprising M1/M4 muscarinic agonist xanomeline and a peripheral muscarinic inhibitor tropsium, was recently investigated in a phase 2 trial for safety in humans (Correll et al., 2022). Future studies may effectively use PAMs or this novel drug to probe the effects of muscarinic activation on cognition. At the time of writing, investigations into muscarinic agonists are approached from the view of safety and tolerability in humans.

Results reported here are based on three papers, which analysed a total of three muscarinic agonists: HTL0018318, HTL0009936 and GSK1034702. All are specific M1/M4 receptor agonists. An additional study by Bakker, Tasker, et al. (2021) reported similar outcomes, however it was eventually excluded as outcomes were not subject to formal hypothesis testing. Included studies are powered to detect statistically significant cognitive changes in their sample sizes, but these results are purely preliminary as they were mainly aimed to look at safety and tolerability of the drugs. As such, dosage for all three drugs spanned a wide range. HTL0018318 was dosed at 5 mg, 15 mg and 25 mg, while HTL0009936 was dosed at 13.5 mg, 40 mg and 79.5 mg. GSK1034702 was dosed at 4 mg and 8 mg.

3.3.2.1. Attention. Only one study looked at the effect of muscarinic agonists on attention (Bakker, Prins, et al., 2021). Two tasks measuring sustained attention were administered, namely the adaptive tracking test and the rapid visual information processing task, and both tasks found no effect of HTL0009936 on performance.

3.3.2.2. Perceptual sensitivity. All three studies investigated the effect of muscarinic agonists, utilizing tasks engaging perceptual detection or preattentive change detection, and no effect of muscarinic agonsits were found.

Nathan et al. (2022) found an enhancement in stimuli detection with administration of HTL0018318 while Bakker, Prins, et al. (2021) and Nathan et al. (2013) found no effect with HTL0009936 and GSK1034702 respectively. This disagreement may be drug-dependent, or due to methodological limitations in both studies.

3.3.2.3. Information processing. Two studies observed the effect of muscarinic agonists on information processing and both found no effect (Bakker, Prins, et al., 2021; Nathan et al., 2013).

3.3.2.4. Peripheral side effects. Each study examined the peripheral side effects of administering HTL0018318, HTL0009936 and GSK1034702. All studies reported headaches and nausea as adverse side effects of muscarinic agonist administration, while Nathan et al. (2022) reported gastrointestinal symptoms such as diarrhoea. Bakker, Prins, et al. (2021) further reported increased heart rate and blood pressure with administration of HTL0009936 at 79.5 mg. Nathan et al. (2013) did not report effects on heart rate or blood pressure.

No studies investigating the co-administration of a peripheral side effect inhibitor was studied, likely due to the nature of the investigations which were aimed at establishing safety and tolerability. Previously, Boucart et al. (2015) co-administered domperidone with scopolamine, the muscarinic antagonist, in order to inhibit digestive adverse effects. 0.2 mg of glycopyrrolate was also administered by Furey et al. (2008), Bentley et al. (2003) and Bentley et al. (2004) for the same purpose. The studies did not further report experiences of digestive side effects after administration, but addition of peripheral inhibitors may nevertheless be a potentially valid method of limiting adverse peripheral effects.

3.3.3. Nicotinic antagonists

The nicotinic antagonist mecamylamine was most commonly studied in terms of its effects on human cognition. It is nonselective and noncompetitive, and was traditionally used as an antihypertensive agent before being discontinued due to ganglionic side effects (Bacher et al., 2009). Dosages administered in this review ranged from 10 mg to 30 mg, and were blanket administered at the same level to all participants except in Little et al. (1998) and Voss et al. (2010), which were given at a weight-dependent dose of 0.2 mg/kg to a maximum of 15 mg. Only one other study administered memantine, an N-methyl-D-aspartate glutamate receptor antagonist that has been shown to be able to block α7 nicotinic receptors at low doses (Aracava et al., 2005; Bali et al., 2019). Memantine was administered at 20 mg.

3.3.3.1. Attention. A total of six studies looked at the effects of nicotinic antagonists on attention, five of which investigated sustained attention specifically. Results were inconclusive with regard to sustained attention, and pointed to no effect on alerting, orienting or executive function.

In the sole study investigating alerting, orienting and executive attention, no effect of mecamylamine was found (R. Thienel et al., 2009). Of the remaining studies, three observed reductions in sustained attention (Alvarez-Jimenez et al., 2018; Baakman et al., 2017; Roh et al., 2014), and no effect was found in the remaining two (Ellis et al., 2006; Yuille et al., 2017). Interestingly, studies that observed an effect of mecamylamine on sustained attention utilized less cognitively complex tasks (eg. adaptive tracking test, 'Identical Pairs' continuous performance test) compared to tasks that found null effects, such as the Rapid Visual Information Processing task. This suggests that task differences may have contributed to this inconsistency.

3.3.3.2. Perceptual sensitivity. Six studies investigated the effect of mecamylamine on perceptual sensitivity. Discrimination sensitivity and perceptual detection tasks showed conclusive null effects of mecamylamine.

Both investigations on discrimination sensitivity by Ellis et al. (2006); Erskine et al. (2004) found no effect of drug administration on discrimination sensitivity using the critical flicker fusion test, which established participants' frequency threshold for perception of visual flickering. For perceptual detection tasks, impairments were reported in two studies (R. Thienel et al., 2009; Thompson et al., 2000) but were not observed in four tasks (Alvarez-Jimenez et al., 2018; Ellis et al., 2006; Erskine et al., 2004; Yuille et al., 2017). This discrepancy could not be attributed to drug dosage or task requirements.

3.3.3.3. Belief adaptation. Three studies investigated the effect of nicotine antagonists on belief adaptation. Two studies utilizing the repeated acquisitions test administered mecamylamine, and found a reduced effect of learning (Newhouse et al., 1992, 1994).One study administered memantine, and reported no effect on an item-category association task (Becker et al., 2013).

3.3.3.4. Information processing. The role of mecamylamine on information processing was observed in three studies administering mecamylamine, and results partially supported involvement of nicotinic receptors in processing speed.

Two studies found a reduction in speed using spatial rotation tasks (Newhouse et al., 1992, 1994). On the other hand, Voss et al. (2010)

found no effect of mecamylamine on information processing with the Trail-Making Task and the Tower of London. Given the differences in cognitive requirements of the administered tasks, discrepancies in the observed cognitive effects may be accounted for by the differing cognitive complexities required by the administered tasks.

3.3.3.5. Behaviour inhibition. Six studies were conducted investigating the role of mecamylamine on behaviour inhibition, and produced conflicting evidence.

Newhouse et al. (1992) and Newhouse et al. (1994) both observed a reduction in speed on the choice reaction time task with mecamylamine administration, while Ellis et al. (2006), Potter et al. (2012) and Roh et al. (2014) found no effect. Baakman et al. (2017) found an increase in body sway indicating reduced behaviour inhibition with mecamylamine, but interestingly observed an increase in speed on the Stroop task with no corresponding effects on accuracy.

3.3.3.6. Action preparation. Two papers studied the effects of mecamylamine on action preparation using the finger tapping test (Alvarez-Jimenez et al., 2018; Baakman et al., 2017). Both observed a reduction in performance.

3.3.3.7. Peripheral side effects. Peripheral side effects of mecamylamine were recorded in four studies. Alvarez-Jimenez et al. (2018), Little et al. (1998) and Thompson et al. (2000) found increases in pulse with mecamylamine administration, while Yuille et al. (2017) did not find any changes. This effect appears to be dose-dependent, as Yuille et al. (2017) administered doses of mecamylamine up to 1.2 mg, whereas Alvarez-Jimenez et al. (2018), Little et al. (1998) and Thompson et al. (2000) administered doses ranging from 13.5 mg to 30 mg. Mecamylamine was also shown to decrease blood pressure in two studies (Alvarez-Jimenez et al., 2018; Little et al., 1998) but not in others (Thompson et al., 2000; Yuille et al., 2017). This may be attributable to blood pressure being taken when standing or when supine, as both Alvarez-Jimenez et al. (2018) and Little et al. (1998) reported that standing blood pressure was significantly affected by mecamylamine, but not supine blood pressure. The posture of participants when obtaining blood pressure was not reported in Thompson et al. (2000) and Yuille et al. (2017).

3.3.4. Nicotinic agonists

Nicotine, a nonselective nicotinic receptor agonist, was the primary drug used to stimulate nicotinic receptors, investigated in all but five studies. Three of the five remaining studies investigated the effects of CDP-choline (Choueiry et al., 2020; Knott, de la Salle, et al., 2015; Knott, Impey, et al., 2015) and one investigated the effect of varenicline (Roh et al., 2014). Varenicline is an α4β2-specific agonist and exerts its effects only in the brain, whereas CDP-choline is an α7-agonist. Nicotine was administered at dosages from 1 mg to 14 mg, with modes of 6–7 mg. CDP-choline was administered at 500 mg only, and varenicline was administered at 1 mg.

3.3.4.1. Attention. Conflicting evidence was found for the effect of nicotinic agonists on attention, with results pointing to a more significant role of nicotinic agonists on sustained attention compared to selective attention, and an inconclusive role in attentional control.

Within the 17 studies investigating the effect on attention, eight tasks found increases in speed or performance (Barr et al., 2008; Breckel et al., 2015; D'Souza et al., 2012; Hahn et al., 2020; Knott et al., 2012, 2011; Meyhöfer et al., 2019; Pham et al., 2020), and seven tasks found no differences in speed or performance with nicotine administration (Ahrens et al., 2015; Behler et al., 2015; Impey et al., 2013; Knott et al., 2009; Roh et al., 2014; Shah et al., 2011; Smucny et al., 2016). The remaining two tasks reported contrasting effects of nicotine. Ettinger et al. (2017) reported attentional enhancements with the continuous performance task but no effect on alerting, orienting or executive attention, and similarly Wignall and de Wit (2011) reported a reduction in orienting attention with nicotine administration but no effect for the alerting effect, conflict effect or overall accuracy (Wignall and de Wit, 2011). This finding was acknowledged by the authors as potentially spurious.

By attention subtype, eight of the 10 studies utilising tasks involved in sustained attention reported significant increases in attention performance. On the other hand, all but one study investigating selective attention (e.g. using visual search tasks) reported no effects on attentional performance. Attentional allocation tasks were not as clear-cut, with Hahn et al. (2020) finding performance enhancements with nicotine administration but Impey et al. (2013) observing no changes in performance.

Interestingly, several studies found modulators of the effect of nicotinic agonists on attention. For example, Ahrens et al. (2015) observed that nicotine was able to enhance performance on conditions with incongruent distractors in a visual search task in DRD2 CC/CHRNA4 C+ carriers compared to other genotypes. In a similar task, Behler et al. (2015) found that in participants with low baseline performance, administration of nicotine was able to reduce distractor effects and enhance performance on a visual search task. This suggests that the effect of nicotine on attention may be dependent on individual differences, and generally masked in population studies, in line with the findings of inverted U-shaped relationships of cholinergic signalling with attentional task performances (Cools and Arnsten, 2022).

3.3.4.2. Perceptual sensitivity. In total, 18 studies sought to examine the effects of nicotinic agonists on perceptual sensitivity. Evidence tended towards supporting a lack of nicotinic influence on all perceptual sensitivity subtypes.

13 studies observed no changes in perceptual sensitivity performance (Ahrens et al., 2015; Behler et al., 2015; Choueiry et al., 2020; Ettinger et al., 2017; Impey et al., 2013; Knott, Choueiry, et al., 2014; Knott, de la Salle, et al., 2015; Knott, Impey, et al., 2015; Knott, Impey, et al., 2014; Knott et al., 2012; Shah et al., 2011; Sun et al., 2021; Wignall and de Wit, 2011). Five studies reported significant effects (Breckel et al., 2015; Hahn et al., 2020; Harkrider and Hedrick, 2005; Meyhöfer et al., 2019; Pham et al., 2020).

Assessing by task subtype, 12 tasks were used to examine perceptual detection, and four studies found increases in perceptual detection abilities. Five tasks observed effects of nicotine on preattentive sensory change detection, with only one reporting performance enhancements (Harkrider and Hedrick, 2005). The remaining eight tasks investigated the role of nicotinic agonists on discrimination sensitivity using tasks establishing 'just noticeable difference' thresholds, with three studies reporting significant effects.

3.3.4.3. Belief adaptation. Belief adaptation was assessed in three studies, and no effect of nicotine was found. Two studies found no effect on cue-target detection time (Thiel and Fink, 2008; Thiel et al., 2005). Vossel et al. (2008) found a reduced effect on location cueing.

3.3.4.4. Information processing. Processing speed was assessed in three studies and found to have no effect. Barr et al. (2008) and Knott et al. (2009) observed no changes in information processing, while D'Souza et al., (2012) reported reductions in speed.

3.3.4.5. Behavioural inhibition. 10 studies investigated the effect of nicotinic agonists on behavioural inhibition, and results did not support an effect. Seven studies found no effect of nicotinic agonists on behavioural inhibition on a wide range of tasks, such as the choice reaction time task, Stroop task, go/no-go task, flanker task etc. (Ahrens et al., 2020; Barr et al., 2008; Ettinger et al., 2017; Kasparbauer et al., 2019; Knott, de la Salle, et al., 2015; Petrovsky et al., 2012; Roh et al., 2014).

Several studies reported conflicting effects: D'Souza et al., (2012) found no effect of nicotine on a choice reaction time task, but a reduction in performance on a Stroop-like task. Similarly, Wignall and de Wit (2011) reported no effect on a stop signal task but an increase in performance on a Stroop task, and Potter et al. (2012) reported no effect on a choice reaction time task but an increase in performance on a stop signal task.

3.3.4.6. Action preparation. Only one study observed the effect on action preparation. D'Souza et al., (2012) found no effect on the finger tapping task.

3.3.4.7. Peripheral side effects. Nicotine was reported to significantly increase pulse rate, or at least reduce the decrease in heart rate compared to placebo, in 11 studies (Ahrens et al., 2015; Behler et al., 2015; Choueiry et al., 2020; Hahn et al., 2020; Impey et al., 2013; Pham et al., 2020; Shah et al., 2011; Thiel et al., 2005; Vossel et al., 2008; Wignall and de Wit, 2011), while no effects on pulse rate were found in four studies (Knott, Choueiry, et al., 2014; Knott, Impey, et al., 2014; Knott et al., 2009; Sun et al., 2021). Evidence for the effect of nicotine on blood pressure was less conflicted: seven studies reported no change in blood pressure (Behler et al., 2015; Breckel et al., 2015; Impey et al., 2013; Knott, Choueiry, et al., 2014; Knott, Impey, et al., 2014; Knott et al., 2009; Smucny et al., 2016) but two studies found an increase in blood pressure with nicotine (Ahrens et al., 2015; Hahn et al., 2020). CDP-choline was not associated with changes in heart rate or blood pressure (Choueiry et al., 2020; Knott, de la Salle, et al., 2015; Knott, Impey, et al., 2015).

3.3.5. General agonists

Instead of specific investigations on nicotinic and muscarinic receptors, some studies investigate general cholinergic signalling. This is most commonly done using cholinesterase inhibitors that increase the basal level of ACh for non-specific stimulation of both nicotinic and muscarinic ACh receptors. The two main agonists found in this form of investigations are galantamine and donepezil. Three studies (Bentley et al., 2004, 2003; Furey et al., 2008) investigated the effect of physostigmine, but this drug is not widely utilised due to its high toxicity in humans. In all three studies, glycopyrrolate, a peripheral muscarinic antagonist, was administered to counter the side effects in participants.

Donepezil was dosed at 5 mg, while galantamine was dosed at ranges of 4 mg – 16 mg. Physostigmine was continuously dosed for 40 min at rates of 1.93 mg/h for 10 min and 0.816 mg/h for 30 min, with a maximum of 1.3 mg.

3.3.5.1. Attention. Attention was measured by seven studies, and an overall role of ACh in attentional enhancement was not supported.

Six studies showed no effect of general agonists on attention (Bentley et al., 2004, 2003; Bunzeck et al., 2014; Chamoun et al., 2017; Furey et al., 2008; Kosovicheva et al., 2012), and only Rokem et al. (2010) found increases in voluntary attention with administration of donepezil. Inherent differences in drug effectiveness may be relevant for the result inconsistency, as Rokem et al. (2010) administered donepezil, which was only administered in one other study (Chamoun et al., 2017). The remaining studies reporting no effect administered physostigmine (Bentley et al., 2004, 2003; Furey et al., 2008) and galantamine (Bunzeck et al., 2014).

3.3.5.2. Perceptual sensitivity. Perceptual sensitivity was assessed in 11 studies, and a role of ACh was not strongly supported in perceptual detection, discrimination sensitivity or preattentive sensory novelty detection.

No effect was found in eight of the studies (Boucart et al., 2015; Bunzeck et al., 2014; Byrne et al., 2020; Chamoun et al., 2017; Hahn et al., 2020; Kosovicheva et al., 2012; Rokem et al., 2010; Rokem and Silver, 2010), of which three tasks measured detection abilities and five investigated visual discrimination capabilities. The remaining three studies reported increases in perceptual sensitivities (Bentley et al., 2004; Gratton et al., 2017; Moran et al., 2013), using tasks measuring perceptual detection, discrimination sensitivity and sensory novelty processing respectively.

Interestingly, one study reported increased learning effects with administration of cholinergic agonists (Rokem and Silver, 2010), supporting a role for ACh in modulating perceptual learning in combination with evidence from Bliem et al. (2008) showing reduced perceptual learning effects with scopolamine administration. This is also in line with evidence that ACh plays an important role in memory, which as mentioned earlier is not covered in this review.

3.3.5.3. Belief adaptation. General agonists did not significantly affect the rate of belief adaptation (Iglesias et al., 2021; Vossel et al., 2014). However, Vossel et al. (2014) further investigated the effect of galantamine on the influence of probabilistic contexts in response speeds and found that galantamine increased this influence. The authors explained this effect through a dose-dependent increase in speed of updating of beliefs, resulting in an increased learning rate.

3.3.5.4. Information processing. Two studies observed the effect of administration of general agonists on information processing speed, and general agonists were found to not affect processing speed. Nathan et al. (2001) found no effect on the trail-making test, and Furey et al. (2008) similarly found no changes in accuracy or speed in a multiple object tracking task.

3.3.5.5. Peripheral side effects. Peripheral side effects were mostly reported in studies investigating galantamine administration, and with conflicting evidence. Hahn et al. (2020) found that galantamine was not associated with changes in pulse rate, whereas Vossel et al. (2014) reported a reduction in the decrease in heart rate in the galantamine-administered group compared to placebo. This effect may be due to differences in dosage, as the 4 mg dosage administered in Hahn et al. (2020) is much lower than the 8 mg administered in Vossel et al. (2014). Both studies also reported that galantamine did not affect blood pressure. A single study reported side effects of administration of donepezil, and found no effects of the drug on heart rate or blood pressure (Bentley et al., 2003). The same study also administered 0.2 mg of glycopyrrolate to target peripheral cholinergic receptors and limit gastrointestinal side effects. Effects of glycopyrrolate administration were not reported in the study.

4. Discussion

This review sought to establish the role of ACh on various cognitive processes, stratified by receptor type as investigated using pharmacological modulators. Key findings suggest that muscarinic antagonists reduce sustained and executive attention but not selective attention. They also impair perceptual detection, and blunt the acquisition rate of cue-response relationships. By contrast, nicotinic antagonists impair associative learning, information processing speeds and action preparation speeds. Nicotinic agonists only enhance sustained attention. Lastly, general agonists do not affect any of the cognitive domains tested. Conclusions related to muscarinic agonists are limited by study design limitations and the lack of available appropriate agents. In addition, given the remarkable speed and affinity of acetylcholinesterase to ACh (Sarter and Lustig, 2020), acetylcholinesterase-activating agents are not widely used, and general cholinergic antagonists were not identified or reviewed in this study.

4.1. ACh is able to regulate the prioritization of top-down versus bottom-up information in perceptual inference

Cholinergic signaling has been observed to induce selective, region-specific effects (Hasselmo and Giocomo, 2006; Picciotto et al., 2012), allowing ACh to differentially enhance or suppress inputs (Bentley et al., 2011; Minces et al., 2017). Through this mechanism, ACh acts to integrate neural activity from cortical feedback or sensory feed-forward streams and thus control the relative influence of each for sensory inference (Yu and Dayan, 2002). As a corollary, computational studies have also proposed that ACh can signal the level of confidence in the validity of prior predictive relationships (Yu and Dayan, 2002, 2005). Findings of this review partially support this current understanding of the role of ACh in cognition: cholinergic modulators tuned information processing speed and perceptual detection ability, as well as attentional control processes and the speed of belief adaptation. The findings paint a picture of cholinergic-regulated redistribution of cognitive resources for enhancement of bottom-up perceptual processing at the expense of top-down expectations.

Given our specific interest in the role of ACh in situational-driven behaviour updating, one primary aim of this review was to collate human evidence for the influence of ACh on cue probability PE precision. Rooted in the Bayesian brain theory, PEs are a feature of predictive coding cognition models, which suggest that animals (human and non-human) have an internal model of the world characterized by beliefs that are used to predict their environment (Mathys et al., 2014). Predictions are based on a prior probability distribution estimated by the agent, but estimation of this distribution is complicated by two forms of uncertainty: uncertainty about the predictive potential of cues (expected uncertainty), or uncertainty about the stability of the environment (unexpected uncertainty). In order to take this uncertainty into account, updating of cue validity beliefs are suggested to be dependent on the precision weights of sensory probability PEs. A number of studies have confirmed a relationship between ACh and higher-level PE signaling (Kocagoncu et al., 2021; Pérez-González et al., 2024). ACh levels have also been hypothesized to represent uncertainty in the predictive validity of top-down expectations (Yu and Dayan, 2005), culminating in the possibility that ACh could represent the precision term in weighted PEs that affect speeds of belief updating in the face of uncertainty. Results of this review support such a proposal, and provide evidence that antagonists at muscarinic receptors did not just inhibit the acquisition of new associative relationships, but in fact impaired implicit validity belief changes. All studies but one investigating effects of ACh on high-level contingency PE signaling reported in this review found effects of their respective modulator on signaling PE precision. Vossel et al. (2014) observed faster belief updating with galantamine administration, a result attributed to increasing the weight of sensory evidence in determining the precision of contingency PEs. Marshall et al. (2016) and Iglesias et al. (2021) also found slower belief updating with biperiden, attributed to reduced precision weighting of the contingency PEs. However, while ACh's role in signaling expected uncertainty suggests pharmacological-associated modulation of only higher order contingency PEs rather than sensory PEs themselves (ie. rate of change rather than change itself), both Iglesias et al. (2021) and Moran et al. (2013) also show modulation of the low-level sensory PEs. For example, Moran et al. (2013) reported enhanced precision of sensory PEs with galantamine. Such effects may be explained by effects of cholinergic signaling on the dopaminergic network, which has been suggested to specifically regulate PEs about sensory outcome (Iglesias et al., 2021), as well as the simpler prediction model used in Moran et al. (2013), which may not have been able to distinguish the hierarchical relationship of PEs. Deeper investigation is thus warranted to determine spuriousness of findings, or to adjust the current hypothesis of ACh to accommodate low-level PE signaling.

Studies that utilize the probabilistic Posner cue task provide another source of support for the role of ACh in PE signaling albeit with one moderating factor. The Posner task (Posner et al., 1980) presents participants with a visually predictive relationship where a cue signals the location of a subsequent target stimuli with a certain probability. Participants generally process correctly cued trials faster than incorrectly cued trials, and the difference is known as the validity effect, which varies with cue validity. ACh is known to be inversely correlated with the validity effect, in line with the prediction that high ACh levels signify high uncertainty in a known cue relationship, resulting in a greater prioritization of bottom-up sensory input and a smaller validity effect (Phillips et al., 2000). However, Vossel et al. (2008) reported that for cue validities below 60 %, a change in the validity effect could not be observed by modulation of cholinergic transmission. This is suggested to be due to a ceiling effect stemming from the baseline lack of confidence in the cue relationship. In line with this, of the other four studies that assessed performance in the Posner task, two studies with validities above 60 % found a reduction of the validity effect with nicotine administration (Breckel et al., 2015; Thiel and Fink, 2008), while the remaining two used validities below 60 %, and did not find an effect (Impey et al., 2013; Laube et al., 2017).

4.2. No clear human evidence for functional distinctions between muscarinic and nicotinic receptor-acting agents

In this review, differences in cognitive effects were found between muscarinic and nicotinic modulators in line with the literature: nicotinic modulators affected motor function and sustained attention (Hahn, 2015; Terry et al., 2023), while muscarinic modulators regulated executive attention (Chen et al., 2004). Beyond these basic cognitive functions, findings from animal studies further suggest a systems level integration of both muscarinic and nicotinic signaling on cognition. Excitation of muscarinic receptors have been shown play more of a role in suppressing top-down information, whereas nicotinic excitation is more responsible for facilitation of bottom-up information (Hasselmo and Giocomo, 2006; Hasselmo and Sarter, 2011; Kunnath et al., 2023; Fernandez de Sevilla et al., 2021). This is supported by brain slice recordings, which show nicotinic-driven enhancement of thalamocortical input (Gil et al., 1997; Lee et al., 2015). A passive sound processing study in mice which investigated the role of muscarinic receptors similarly showed its relevance in mediating intracortical signaling and connectivity (James et al., 2019).

However, conclusions from this review suggest that such a claim may not be valid in humans. Functions traditionally viewed as bottom-up-dominant such as perceptual sensitivity or belief adaptation were seen to be associated with muscarinic but not nicotinic modulators, as neither nicotinic antagonists nor agonists evoked a significant change in perceptual detection tasks, while muscarinic antagonists impaired detection performance. Attentional reorienting, thought to be a nicotinic-driven task (Thiel et al., 2005), was also not significantly influenced by nicotinic modulators, agonistic or antagonistic, in this review. Nevertheless, given that in vivo animal studies have the capacity to be much more rigorous in probing specific receptors compared to human studies, such a discrepancy may not suggest inaccuracies in the current literature, and simply highlight the need for greater specificity in human ACh studies.

4.3. Limitations of pharmacological studies

A primary concern about current human cholinergic drugs is that they lack specificity needed to test detailed hypotheses derived from animal studies. For instance, memantine, which was administered by Becker et al. (2013) as a nicotinic antagonist, has strong off-target effects at NMDA receptors (Gilling et al., 2007, 2009), clouding our interpretation of the role of cholinergic signaling in cognition. Scopolamine, a nonspecific muscarinic antagonist, also has the ability to activate unblocked nicotinic receptors via concurrent stimulation of inhibitory M2 receptors (Hasselmo and Sarter, 2011). Non-specific receptor

inhibition could have thus reduced the sensitivity of investigations, inappropriately implicating muscarinic antagonism in enhancement of feedforward cortical inputs. Further supporting this, general cholinergic agonists were found to have no significant effect on any cognitive domain whatsoever. This suggests that specific stimulation of receptors is critical for the effects of ACh on cognition, and is supported by studies showing differential downstream molecular effects with administration of general acetylcholinesterase inhibitors compared to specific receptor-acting agents. For example, acetylcholinesterase inhibitors have been shown to significantly modulate septohippocampal GABAergic neurons over cholinergic neurons (Wu et al., 2003) and its cognitive impact in healthy adults is reported to be limited by ceiling effects of endogenous ACh (Morasch et al., 2015).

As a corollary, receptor subtype-specific cognitive effects also have been found for both muscarinic and nicotinic receptor signaling. Prior animal investigations show that α4β2* receptor agonists are more strongly associated with attentional performance enhancement (Hahn, 2015) than nicotine alone, a conclusion we are unable to corroborate due to the overwhelming use of nicotine found in this review. In terms of muscarinic receptor subtypes, differences in cognitive roles of the different muscarinic receptor subtypes have been well-established in the animal literature with some translation into human memory studies. Biperiden, specific to M1 receptors, is generally found to have a more isolated effect on learning and memory compared to the nonspecific scopolamine (Klinkenberg and Blokland, 2011; Miravalles et al., 2025), sparing cognitive functions like attention and information processing (Blokland, 2022; Naseri et al., 2023). Such findings are consistent with studies showing a high expression of M1 receptors in the hippocampus (Brown et al., 2021) as well as a lack of M1 receptor involvement in observable perceptual processes (Kang et al., 2015). Although memory was outside the scope of this review, results were partially in line with the literature, as scopolamine impaired perceptual performance while biperiden did not, though no drug differences were found in sustained attention. However, while preliminary human data agrees with the literature, the lack of receptor subtype-specific pharmacological modulators in human studies precludes muscarinic receptor subtype-level conclusions. Currently, only biperiden and scopolamine are regularly used as subtype-specific drugs, however cognitive differences may have arisen from other factors such as drug pharmacokinetics rather than solely receptor selectivity. For example, though both biperiden and scopolamine inhibit muscarinic receptors competitively, biperiden has been suggested to be able to bind irreversibly to the muscarinic receptor, which may be responsible for some of its differential cognitive effects (Kimura et al., 1999). Future studies focusing on PET scans with receptor subtype-specific tracers or novel receptor subtype-specific pharmacological agents are necessary to present more converging evidence, and more rigorous investigation into receptor subtypes are needed to disentangle the individual roles of each subtype.

The most glaring limitation of pharmacological investigations lies in the fact that neuromodulation is unable to fully mimic in vivo signaling of ACh (Hasselmo and Sarter, 2011), which possess both transient and tonic neural communication features. This is especially so for receptor agonists, which constitutively activate receptors and are not able to regulate signaling on a rapid temporal scale. Current literature places the critical role of regulating performance of certain cognitive tasks such as cue detection on transient ACh signaling (Sarter and Lustig, 2020). This conclusion was drawn on the basis that cholinergic neurons spike only when cues were detected by the animal, and pharmacological attempts to restore attentional impairments from cholinergic lesions were not successful (Hasselmo and Sarter, 2011; Parikh et al., 2007). Receptor agonists may not be able to successfully mimic the cognitively useful aspects of in vivo cholinergic neurotransmission and thus may not be useful in determining its effects on human cognition. Instead, the same study proposed that tonic ACh signaling modulates glutamatergic neurotransmission, though this only involves the α4β2* nicotinic receptors (Hasselmo and Sarter, 2011). This is part of a broader hypothesis which suggests that upon tonic nicotinic stimulation of glutamatergic neurons, glutamate release can in turn activate cholinergic neurons to trigger the transmission of ACh transients that directly enhance cue detection. However, given the spatially and subtype-nonspecific nature of currently utilized human pharmacological agents, as seen in this review, investigations are as yet unable to validate this theory much less differentiate the direct effect of ACh from the indirect, glutamate-dependent effect. As such, pharmacological investigations in the current form may not be the most ideal study design in determining the intricacies of cholinergic mechanisms of cognitive control. Future studies may thus require designs accounting for drug pharmacokinetics and pharmacodynamics, including systematic investigations of dose-response and route of administration differences (such as measurement of plasma levels of drugs). The studies in this review did not show a consistent effect of drug dosage and route of administration on cognition or peripheral side effects.

Alternatively, studies can further capitalize on strengths of human neuroscience methods, such as large network dynamics and multimodal data acquisitions, combining in vivo neurochemical and other imaging technologies. For example, human studies with functional magnetic resonance spectroscopy (fMRS) suggest a regional functional dissociation of cholinergic involvement in perceptual attention (in the cortex; Lindner et al., 2017) versus belief updating (in the basal ganglia; Bell et al., 2018; Williams and Christakou, 2022). The combination of pharmacological magnetic resonance imaging with neurostimulation techniques could shed light on the effects of cholinergic modulators on network function and dynamics. These approaches can seed the development of complex models of whole-brain pharmacodynamics.

Aside from pharmacological issues, a final point of discussion pertains to the focus of our review on cognitive domains relevant for acute behavioural updating. As a result, certain cognitive domains were excluded, including perceptual learning and other longer term memory domains. It is worth noting that preliminary evidence suggests that ACh may play a role in enhancing perceptual learning, as well as decision-making. Both classical inference and Bayesian studies showed a significant modulation of ACh agents on perceptual learning rate (Vossel et al., 2014; Marshall et al., 2016; Bliem et al., 2008; Rokem and Silver, 2010), recapitulating previous studies implicating ACh in sensory learning (Kang et al., 2014; Wilson et al., 2004). Despite a lack of evidence for an effect on discrimination sensitivity, ACh may thus be able to influence sensory detection thresholds over time, through repetitive training and enhancement of cortical plasticity and neuronal connectivity. In addition, studies investigating the influence of ACh on cost-benefit decision making in humans were excluded from this review because they were exceedingly rare. However, results of this review ascertained the role of cholinergic regulation in sustained attention, perceptual detection and belief adaptation, all of which allow the agent to gather more accurate information about the current context useful for cost-benefit analysis (Chebolu et al., 2022). Recently, Sidorenko et al. (2023) reported that administration of nicotine in a human sample reduced behavioural deviation from foraging optimality, essentially leading them to ‘make better decisions’. Further investigations validating this relationship are undoubtedly necessary to fully understand the context-specific function of cholinergic signaling on behaviour.

To our knowledge, this is the first comprehensive systematic review investigating the effects of cholinergic modulations on a broad range of cognitive tasks relevant to acute behaviour in humans. Previous reviews have covered roles of acetylcholine in sensory plasticity (Kunnath et al., 2023), cognitive flexibility (Prado et al., 2017), memory (Haam and Yakel, 2017; Huang et al., 2022), and attention (Klinkenberg et al., 2011), however none have done so in a systematic manner, or from the perspective of understanding nonpathological human behaviour. By taking a systems-level approach, our review assesses cognition as the integration of multiple receptor subtypes, and allows us to better understand the cholinergic effect on behaviour. Through consolidation of studies performed in humans, this paper further contributes to our

understanding of the short-term cognitive effects of ACh in human systems that can directly affect decision-making and acute situational behaviour. It is also able to extend knowledge on the available pharmacological methods of cholinergic neuromodulation, paving the way for future studies intending to manipulate cholinergic levels in humans to investigate their effects.

5. Conclusion

This review provides evidence from human investigations that ACh is involved in processes of sustained attention, perceptual detection, speed of information processing and belief adaptation, including the signaling of expected uncertainty via the precision weights of PEs. Together the findings support the role of cholinergic signaling in cognitive functions relevant for rapid behavioural adaptation, complementing its previously established well-known role in memory processes. On the other hand, limited evidence is presented implicating ACh in action preparation and behavioural inhibition. The independence of nicotinic and muscarinic receptor effects is not substantially supported by results from this review, but could potentially be explained by methodological issues. Finally, pharmacological models of cholinergic signaling would benefit by increasing specificity of cholinergic interventions for receptor subtypes. Investigation into a wider variety of cognitive domains (eg. perceptual learning and decision making) would also be useful for the understanding of neuromodulation in behavioural adaptation.

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Declaration of Competing Interest

The authors have no competing interests to declare.

Appendix A. Supporting information

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