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Noradrenergic and cholinergic systems take centre stage in neuropsychiatric diseases of ageing

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ABSTRACT

Noradrenergic and cholinergic systems are among the most vulnerable brain systems in neuropsychiatric diseases of ageing, including Alzheimer's disease, Parkinson's disease, Lewy body dementia, and progressive supranuclear palsy. As these systems fail, they contribute directly to many of the characteristic cognitive and psychiatric symptoms. However, their contribution to symptoms is not sufficiently understood, and pharmacological interventions targeting noradrenergic and cholinergic systems have met with mixed success. Part of the challenge is the complex neurobiology of these systems, operating across multiple timescales, and with non-linear changes across the adult lifespan and disease course. We address these challenges in a detailed review of the noradrenergic and cholinergic systems, outlining their roles in cognition and behaviour, and how they influence neuropsychiatric symptoms in disease. By bridging across levels of analysis, we highlight opportunities for improving drug therapies and for pursuing personalised medicine strategies.

1. Introduction

Acetylcholine and noradrenaline are neuromodulators that support many of the neurocognitive functions required for adaptive cognition and behaviour. From the 1960s and 1970s, both Alzheimer's and Parkinson's disease were shown to cause depletion of these neuromodulators, due to neuropathology within their attendant subcortical nuclei (Bowen et al., 1976; Davies and Maloney, 1976; Ehringer and Hornykiewicz, 1960; Farley and Hornykiewicz, 1976; Ishii, 1966). This work sparked hypotheses of a shared vulnerability in these diseases affecting neurons of the reticular formation, or isodendritic core, of the brain – namely, brainstem and basal forebrain regions housing the subcortical nuclei of the ascending arousal system (Rossor, 1981). A new era of drug therapies began: cholinergic drugs for Alzheimer's disease that remain the mainstay of treatment (Contestabile, 2011), and noradrenergic drugs that initially fell out of favour but which have since had resurgent interest and signals of efficacy (David et al., 2022).

Despite this longstanding evidence, the roles of these ascending neuromodulators in cognitive and psychiatric symptoms is sometimes overlooked (Grinberg et al., 2011; Theofilas et al., 2015). Part of this neglect may be due to cortico-centric views of cognitive dysfunction, which equate higher order symptoms with cortical pathology. These views may discount how sensitive the cortex is to its neurochemical state, and underestimate the role of ascending neuromodulators in orchestrating both flexibility and precision across the entire brain (Arnsten, 2000; Goldman-Rakic, 1997; Mesulam, 2004; Robbins, 2005). Historically, disproportionate attention has been given to a single system for each major disorder, including the cholinergic system in Alzheimer's disease (Friedman et al., 1999) or the dopaminergic system in Parkinson's disease (Rommelfanger and Weinshenker, 2007). This has

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been at the expense of considering the multisystem nature of these diseases, and appreciating that cognitive and psychiatric symptoms are complex expressions of dysfunction across diverse neuromodulatory systems. Here we address some of this complexity by considering, in tandem, the architecture of the noradrenergic and cholinergic systems; how they modulate behaviour; and the implications for transdiagnostic symptoms in neuropsychiatric diseases of ageing.

Neuromodulatory systems are not synonymous with a single function. Instead, each system exerts varied effects on cognition and behaviour depending on arousal levels, the target structures it modulates, and, the receptor types and locations within those target structures (Trofimova and Robbins, 2016). This exquisite complexity is unmasked by neurodegenerative diseases, where neuromodulatory dysfunction is associated with multidimensional symptoms that often follow a non-linear trajectory over the disease course. These changes may be concealed from clinicians and even the patient themselves for many years, due to endogenous compensatory mechanisms and slow progression. By the time a person seeks medical attention, the underlying pathologies are typically multifocal and moderately severe (e.g., Braak stage 2–4 in mild cognitive impairment due to Alzheimer's disease, against a maximum stage 6). Compensatory processes are overwhelmed, and symptoms become clearer. In the context of progressive multisystem involvement, pharmacotherapy for these diseases must aim at a moving target. With emerging disease-modifying treatments currently having limited clinical efficacy, and not yet in routine clinical practice (Thambisetty and Howard, 2023; van Dyck et al., 2023), drugs that help with specific symptoms remain the cornerstone of treatment for the time being. The cholinergic agents currently used to treat symptoms do not have a clear disease-modifying effect. It is not known whether early and sustained use of noradrenergic drugs might have disease-modifying potential. We discuss the possibility of neuroprotective effects later in the paper, however our primary focus is the role of cholinergic and noradrenergic agents in symptomatic psychopharmacology.

To complicate matters for drugs that work by restoring neurotransmitter function, neuropsychiatric diseases of later life present with considerable clinical and pathological heterogeneity. Individual differences in pharmacokinetics are also prominent, adding to variability in drug response. This calls for an individualised approach to psychoactive therapies. Despite insights into the principles of such individualised drug therapy, the evidence and algorithms required for precision medicine of neuropsychiatric symptoms are underdeveloped (Cope et al., 2021; Matthews et al., 2014). Adding to the challenge is the optimal timing of these interventions. Neuromodulatory agents are likely to have limited effect if there is extensive cell death or loss of dendritic spines and receptors (Barcelos et al., 2018) – which occur both with disease progression and ageing. Here, we focus on the cholinergic and noradrenergic systems because of their early and prevalent involvement across neuropsychiatric diseases of ageing. Moreover, they represent two unique challenges to symptomatic drug treatment: 1) how to optimise the use of cholinergic drugs already in widespread use, but which see limited and unsustained benefits for many people; 2) how to capitalise on a renewed interest in noradrenergic drugs to foster their widespread clinical use.

By putting the noradrenergic and cholinergic systems front and centre we take a close look at their neurobiology, to help explain their involvement in specific cognitive and behavioural symptoms. We emphasise certain characteristics of these systems that are especially relevant to their role in neuropsychiatric symptoms, namely, that they undergo non-linear changes, and they operate across multiple timescales. In doing so, we highlight opportunities for improving drug therapies and for pursuing personalised medicine strategies.

2. Noradrenergic and cholinergic systems and their role in neuropsychiatric symptoms

Alterations in noradrenergic and cholinergic systems occur in each of the major neurodegenerative diseases of ageing, including Alzheimer's disease, Parkinson's disease, Lewy body dementia, frontotemporal dementia and progressive supranuclear palsy. Ascending neuromodulatory systems are characterised by widespread projections emanating from a small number of neurons in the brainstem and basal forebrain (see Fig. 1). These neuromodulators act on receptors at target sites, modulating baseline firing rates in those regions, and increasing (or decreasing) the likelihood of neurons to fire (Harris and Thiele, 2011; Salinas and Thier, 2000). Through volume transmission – non-synaptic diffusion into extracellular space – these neuromodulators can have a broad spatiotemporal influence over target populations (Sara, 2009). Precise control over circuitry (and cognitive operations) may also be achieved via topographic organisation of efferent projections, and selective transmission at the synaptic cleft (Sarter et al., 2014). This enables wide-ranging effects on neuronal activity, whole-brain coordination and network dynamics – adapting brain states in response to external/internal demands and driving specific behaviours, often in response to a changing environment (Cools and Arnsten, 2022; Lee and Dan, 2012; Marder, 2012).

Despite playing specific roles in shaping cognition and behaviour, neuromodulatory systems share certain principles. First, while neuromodulatory projections have widespread innervation across the brain, their action is dependent on the location at which they target and release (Schultz, 2007). Second, these systems have the capacity to self-regulate with terminal specific autoreceptors and negative feedback loops (Cools, 2019). Third, the cognitive and behavioural performance underpinned by these systems has optimal mid-range levels for function. This leads to an inverted-U relationship, whereby too much or too little neuromodulation can impair performance (Arnsten, 1998; Aston-Jones and Cohen, 2005; Robbins, 2000). Finally, these systems are modulated by the very areas that they themselves target: both by receiving reciprocal descending inputs from higher brain regions and by regulation of terminal activity at local cortical circuits via heteroreceptors. These regulatory mechanisms help sculpt precision and functional differentiation in these systems (Robbins and Roberts, 2007; Sarter et al., 2009). Together, principles governing specificity, autoregulation, dose-response curves and top-down modulation are key considerations for optimised pharmacotherapy during disease progression.

2.1. Noradrenergic system

The dorsal noradrenergic ascending system innervates most areas of the brain, with its widespread projections arising from a small pontine nucleus – the locus coeruleus. The locus coeruleus is among the earliest sites of tau and α-synuclein inclusions in Alzheimer's and Parkinson's disease (Braak et al., 2003; Braak and Del Tredici, 2011), harbouring these inclusions and exhibiting dysfunction for many years before cell death occurs (Huynh et al., 2021; Theofilas et al., 2017). Locus coeruleus cell loss in Alzheimer's and Parkinson's disease is earlier and often exceeds that of the other major neuromodulatory nuclei traditionally associated with each disease, nucleus basalis and substantia nigra pars compacta, respectively (Zarow et al., 2003). Locus coeruleus pathology is prominent in other neurodegenerative diseases, including progressive supranuclear palsy, multiple system atrophy and corticobasal syndrome (Benarroch et al., 2002; Eser et al., 2018; Kaalund et al., 2020).

The locus coeruleus lies in the pons, lateral to the fourth ventricle. It is small (~1 × 16 mm in humans), with few noradrenergic neurons (~50,000 in humans). This nucleus gives rise to highly diffuse projections targeting most brain regions, the spinal cord and autonomic nuclei (Samuels and Szabadi, 2008) (Fig. 1a). Such widespread innervation arising from a small number of neurons requires extensive arborisation of axons (Sara, 2009). This broad collateralisation promotes modulation of brain states (Schwarz and Luo, 2015), but there is nonetheless coarse organisation within the locus coeruleus suggesting a topographic arrangement. Sub-populations of locus coeruleus neurons are clustered with respect to their efferent targets, enabling highly

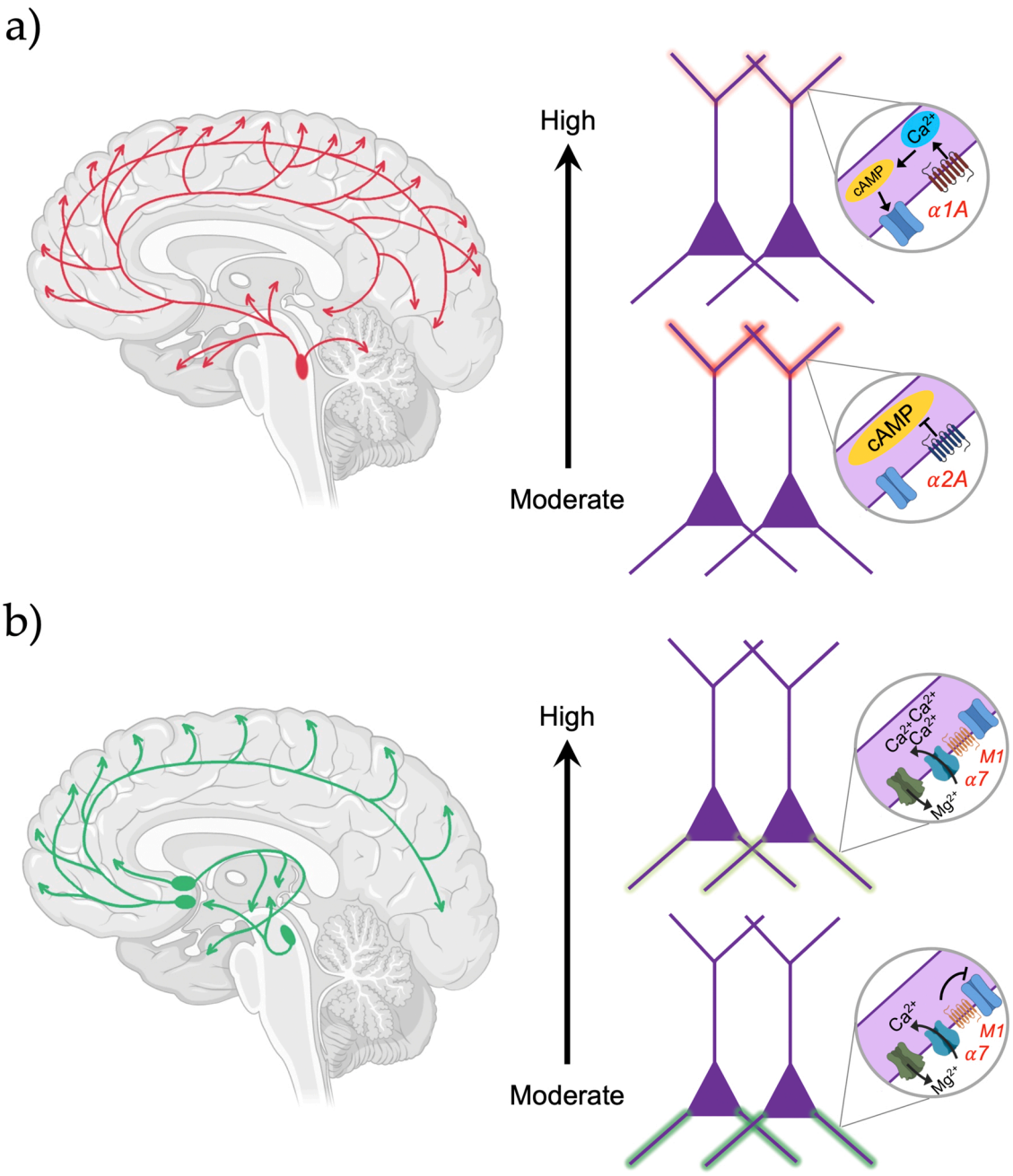

Fig. 1. The noradrenergic and cholinergic systems and their effects on prefrontal cortical circuitry (based on evidence from non-human primates). **a) Noradrenergic system**, from the locus coeruleus (left side panel); Under moderate noradrenaline levels, post-synaptic α2A receptors on dendritic spines are stimulated. This inhibits cAMP and prevents HCN channels from opening, strengthening prefrontal connectivity (Wang et al., 2007). High noradrenaline levels stimulate α1A receptors on post-synaptic dendritic spines, suppressing neuronal firing via activation of calcium–protein kinase C signalling which increases cAMP induced opening of potassium channels (Datta et al., 2019). **b) Cholinergic system**, projections from the basal forebrain, including the septal nuclei (top) and basal nucleus of Meynert (bottom); and from the brainstem pedunculopontine/laterodorsal tegmental complex; Circuity shows the unique role of acetylcholine in modulating persistent firing of pyramidal neurons in layer III dorsolateral prefrontal cortex. Under moderate levels, α7-nAChRs directly flux calcium, relieve the Mg^{2+} block in NMDA receptor pores and depolarise the post-synaptic density to enhance persistent firing (Yang et al., 2013); M1 stimulation contributes to membrane depolarisation and enhanced persistent firing by closing KCNQ K+ channels (Galvin et al., 2020). At higher levels, overstimulation of M1 receptors reduces neuronal firing potentially via excessive calcium-cAMP signalling and opening of KCNQ channels (Galvin et al., 2020; Vijayraghavan et al., 2018); increased α7-nAChR stimulation produces a generalised, non-specific increase in excitability (i.e., on a spatial task neurons no longer selectively fired in their preferred direction, but non-selectively increased their firing for all directions – consistent with a loss of spatial tuning; Yang et al., 2013). Left side panels reprinted from (O'Callaghan et al., 2021c).

selective effects on cognition and behaviour (Poe et al., 2020). For example, distinct sub-populations of locus coeruleus neurons, with different molecular and electrophysiological phenotypes, preferentially project to prefrontal versus motor cortices (Chandler et al., 2014). This organisation allows distinct populations of locus coeruleus neurons to have highly specific effects on brain states (Noei et al., 2022; Totah et al., 2018). Distinct patterns of activity can be seen in these sub-populations during an ongoing task, suggesting that they may play unique roles in executing and refining behavioural output (Breton-Provencher et al., 2022). With respect to topography, Parkinson's disease and Alzheimer's disease lead to differential neurodegeneration of rostral versus caudal locus coeruleus respectively (Theofilas et al., 2017; Ye et al., 2022).

Afferent inputs to the locus coeruleus arise from forebrain and brainstem regions, although these are less globally diffuse than its efferent network (Aston-Jones et al., 1991; Chandler et al., 2019; Schwarz et al., 2015). Many of these inputs do not target the locus coeruleus proper, but rather target the pericoerulear zone, which contains noradrenergic dendrites co-mingled with GABAergic neurons (Aston-Jones et al., 2004; Shipley et al., 1996). Neurons in this pericoerulear zone provide an inhibitory influence over locus coeruleus dynamics (Breton-Provencher and Sur, 2019; Kuo et al., 2020; Luskin et al., 2022). Together, the locus coeruleus and pericoerulear zone receive input from regions involved in executive function, arousal, resource allocation and motivational state (e.g., prefrontal cortex, amygdala, lateral hypothalamus, dorsal raphe and nucleus paragigantocellularis). Afferents from different regions have distinct electrophysiological properties and release probabilities, and they innervate distinct areas of the locus coeruleus. Such modularity of the afferent system further enables the specificity of locus coeruleus-noradrenergic modulation (Barcomb et al., 2022). This afferent-efferent organisation leaves the locus coeruleus-noradrenergic system well placed to integrate rich information about an organism's external and internal environment, and in turn, to influence adaptive behaviours to those environments (Schwarz and Luo, 2015).

The locus coeruleus achieves its widespread influence by releasing noradrenaline to act upon adrenoreceptors. Adrenoreceptors include three major categories – α1, α2 and β – comprising nine subtypes. These are metabotropic, G-protein coupled receptors which activate intracellular second messenger cascades, altering neuronal signalling properties (Thiele, 2013). These receptors differ in their affinity for noradrenaline (α2 > α1 > β) providing another means for noradrenaline to exert selective effects across the brain. For instance, in the prefrontal cortex moderate noradrenaline levels engage post-synaptic α2A receptors on dendritic spines which, via G_i inhibition of cAMP signalling, inhibit opening of HCN channels and strengthen network interactions to facilitate function (Wang et al., 2007) (see Fig. 1a). At higher noradrenaline levels, α1 and β receptors act via G_q /G_s coupling to release intracellular calcium and increase cAMP signalling, respectively. This cascade of cellular processes weakens network connectivity and reduces persistent firing (Datta et al., 2019; Ramos and Arnsten, 2007). Transient increases in noradrenaline that engage α1 and β receptors may also serve to disconnect circuits to permit reorganisation of the network configuration, in order to meet changing environmental demands (Cools and Arnsten, 2022). By contrast, in posterior brain regions including the hippocampus and amygdala, cAMP signalling has the opposite effect of strengthening synaptic connectivity. In these circuits, receptor excitation of cAMP signalling pathways (among others) has enhancing effects, including facilitating long-term depression and long-term potentiation (Arnsten, 2000; Hagena et al., 2016). Noradrenergic activity in specific networks may be further enhanced via local interactions with glutamate, prioritising activity in regions currently engaged by the locus coeruleus-noradrenergic system (Mather et al., 2016).

2.1.1. *Non-linear changes across the disease course*

Non-linear changes occur in the locus coeruleus-noradrenergic system in neurodegenerative diseases of ageing (see Fig. 2) (Gannon and Wang, 2019; Kelberman et al., 2023; Weinshenker, 2018). For example in Alzheimer's disease, pathological tau inclusions arise early in the locus coeruleus even before prodromal mild cognitive impairment stages (Grudzien et al., 2007). Cell loss then occurs with disease progression. However, these inclusions and cell loss are not synonymous with reduced forebrain noradrenaline. While reduced tissue levels of noradrenaline are reported, CSF levels of the noradrenaline metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) indicate higher turnover and increased extracellular availability (Hoogendijk et al., 1999; Palmer et al., 1987). This suggests that surviving locus coeruleus neurons can upregulate their activity, with a compensatory effect (Friedman et al., 1999). Moreover, in Alzheimer's and Parkinson's disease, locus coeruleus hyperactivity occurs before cell death (Weinshenker, 2018). This was recently shown in an early-stage Alzheimer's disease rodent model, where hyperphosphorylated tau is restricted to the locus coeruleus. These animals had locus coeruleus hyperactivity (i.e., increased firing during bursts and in response to footshock stress), in contrast to the later-stage model that had locus coeruleus hypoactivity (i.e., reduced baseline and footshock-response firing) (Kelberman et al., 2023). Other indicators of functional compensation include reduced noradrenaline re-uptake, increased tyrosine hydroxylase mRNA expression and increased noradrenaline synthesis (Gannon and Wang,

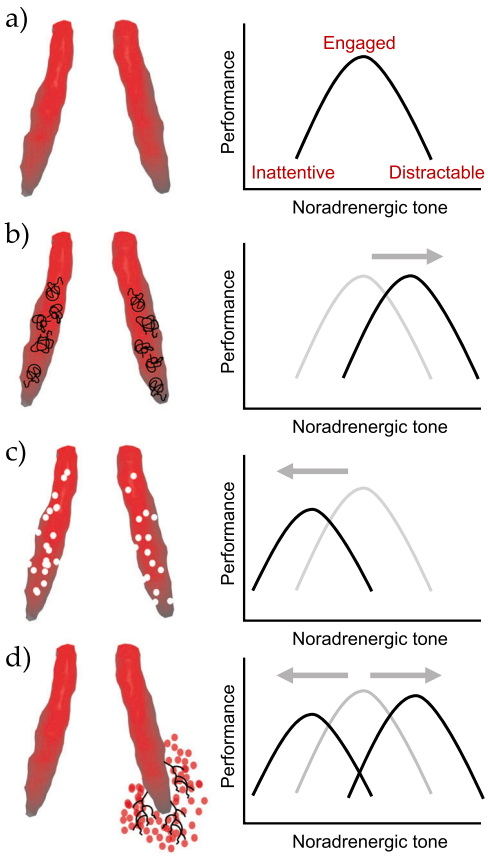

Fig. 2. Schematic view of locus coeruleus changes in neurodegenerative diseases of ageing, and their hypothesised effects on noradrenergic tone and behavioural performance. **a) A healthy locus coeruleus**, where performance can be described by an inverted-U shape. Moderate noradrenaline levels are associated with engaged behaviour and optimal performance on a particular task. Reduced or increased levels are associated with inattention or distractibility, respectively, and impair performance (Arnsten, 1998; Aston-Jones and Cohen, 2005); **b) Pathological inclusions**, where locus coeruleus cells exhibit hyperactivity. This can have a compensatory effect, enabling performance to be maintained at a level similar to that shown in the healthy locus coeruleus. However, there may also be an associated right-ward shift (along the x-axis), whereby the optimal noradrenergic tone for successfully performing a particular task is now increased (David and Malhotra, 2022; Rowe et al., 2008). This may have negative consequences for other behaviours, with too much noradrenaline now impairing performance; **c) Cell loss**, where locus coeruleus activity is decreased. Behaviour is impaired and performance cannot be maintained at heathy levels. A left-ward shift indicates a decreased ability to achieve optimal noradrenaline levels needed for the engaged state, operating instead in a low performing, inattentive mode (David and Malhotra, 2022); **d) Locus coeruleus-pericoerulear dynamics**, neurodegenerative change may involve trimming of the dendritic tree that branches into the pericoerulear zone (Gilvesy et al., 2022), which could reduce inhibitory influence over the locus coeruleus and contribute to hyperactivity; conversely, axonal sprouting into the pericoerulear zone (Szot et al., 2006) could increase inhibitory influence over the locus coeruleus.

2019; Matchett et al., 2021). Compensatory change also manifests micro-structurally. Increased adrenoreceptor expression is observed from the earliest presymptomatic stages of Alzheimer's disease (Andrés-Benito et al., 2017). Ingrowth from sympathetic noradrenergic axons occurs in the hippocampus (Booze et al., 1993; Nelson et al., 2014) and locus coeruleus neurons may sprout noradrenergic axons into the pericoerulear zone and forebrain (i.e., hippocampus and prefrontal cortex) (Szot et al., 2007, 2006). Evidence for noradrenergic axonal sprouting has also been found in dementia with Lewy bodies, but not Parkinson's disease (McMillan et al., 2011).

Hypothetically, these changes that upregulate locus coeruleus-noradrenergic activity could maintain behavioural and cognitive performance, in the face of accumulating pathology (Fig. 2). While direct evidence is lacking for this in humans, the proposal is consistent with mounting evidence that locus coeruleus stimulation can rescue deficits in rodent models of Alzheimer's disease (Omoluabi et al., 2021; Rorabaugh et al., 2017).

Compensatory changes are not unique to the locus coeruleus-noradrenaline system. Indeed, compensation within the dopamine system is a feature of prodromal Parkinson's disease – including increased dopamine metabolism, reduced dopamine transporter expression and stabilisation of dopamine diffusion in the synaptic space (Blesa et al., 2022). And yet, it is important to consider the "double-edged sword" of compensation, as these changes can have both desirable and undesirable consequences. Excessive activation in surviving neurons may contribute to cellular toxicity (Blesa et al., 2017), with increased neuronal activity enhancing tau propagation (Wu et al., 2016), while structural remodelling may provide new routes for pathological spread (Mufson et al., 2015). In this way, compensatory responses to an immediate threat can have longer-term repercussions for accelerating the disease process.

Increased locus coeruleus activity and changes in locus coeruleus-pericoerulear dynamics may help maintain certain behaviours but may also result in noradrenaline levels that are too high for other behaviours, leading to impairment (Fig. 2d). For example, neurodegeneration initially involves trimming of the dendritic tree from neurons in the locus coeruleus core and loss of dendrites branching into the pericoerulear zone (Gilvesy et al., 2022). The loss of α2 autoreceptors on those dendrites then contributes to locus coeruleus disinhibition and hyperactivity. Conversely, putative axonal sprouting into the pericoerulear zone could increase inhibitory influence over the locus coeruleus. In terms of system-level consequences, receptor changes and altered noradrenaline levels at target sites undermine the temporal co-ordination needed to reconfigure brain states to meet changing internal and external demands.

2.1.2. Noradrenergic neuropsychiatric symptoms

Theories of noradrenergic function quickly evolved from a general role in sleep-wake regulation and arousal. The idea of a unitary construct of arousal became untenable (Lacey, 1967; Robbins, 1984), with evidence for a noradrenergic role in sensory processing, attention, learning, memory consolidation and cognitive flexibility (Berridge and Waterhouse, 2003; Sara, 2009). A new overarching theory posited that different modes of locus coeruleus firing balance task engagement versus exploration (Aston-Jones and Cohen, 2005). Phasic firing on a background of moderate tonic levels occurs in response to task-relevant stimuli, promoting sustained attention and exploitation of learned behavioural strategies. Higher tonic levels curb this phasic-to-tonic ratio (required for optimal task engagement), and lead to a disengaged mode in which the organism shifts to explore other states or strategies. This inverted-U relationship between noradrenaline levels and performance can also be seen at the cellular level, for example in the prefrontal cortex of non-human primates performing cognitive tasks. Moderate noradrenaline levels engage α2A receptors, enhancing task-related network activity and improving performance; higher levels engage α1 receptors, supressing task-related firing and impairing performance (Arnsten et al., 2012; Birnbaum et al., 2004; Gamo and Arnsten, 2011; Wang et al., 2007). This is mirrored in the dose-response curves seen in monkeys, where moderate doses of a noradrenaline-promoting drug (atomoxetine) enhanced task performance and task-related neuronal firing, whereas high doses could impair performance and cell firing (Gamo et al., 2010).

Co-ordinated noradrenergic activity at multiple target sites may drive large-scale network reconfiguration – enabling behavioural adaptation in the face of changing environmental contingencies (Bouret and Sara, 2005). The widespread innervation of noradrenaline can support such large-scale changes in brain network organisation (Shine, 2019), which have been observed following locus coeruleus stimulation and noradrenergic reuptake inhibition (Grimm et al., 2022; Oyarzabal et al., 2022; Zerbi et al., 2019). Phasic locus coeruleus firing in response to novelty or salience in the environment biases the organism to detect changing environmental contingencies and adapt behaviour accordingly (Foote et al., 1980; Vankov et al., 1995).

The locus coeruleus-noradrenergic system contributes to a range of cognitive and psychiatric symptoms, across neurodegenerative diseases (David et al., 2022; Holland et al., 2021). The trajectory of noradrenergic dysfunction in these diseases encompasses periods of hyperactivity and slowed dynamics (Fig. 2). This may partly explain why noradrenaline is implicated in seemingly opposite symptoms that nevertheless co-occur in a given individual. Such symptoms represent dynamic, context-sensitive disruptions to a neural system – rather than opposing ends of a static, unidimensional spectrum (Morris et al., 2022; Passamonti et al., 2018; Sinha et al., 2013). A prime example is apathy and impulsivity, which commonly co-occur, and have both been related to the locus coeruleus-noradrenergic system in Alzheimer's, Parkinson's and progressive supranuclear palsy (Cassidy et al., 2022; Hezemans et al., 2022; Madelung et al., 2022; O'Callaghan et al., 2021b; Ye et al., 2022).

The co-occurrence of positive and negative symptoms (e.g., apathy and impulsivity, agitation/anxiety and depression) may reflect a common disruption of the signal-to-noise balance that arbitrates engagement vs. disengagement with the internal vs. external environment. Locus coeruleus *hypoactivity* could reduce exploration of new aspects of the environment, as the required tonic levels to promote flexible behaviour are not achieved. This is consistent with dimensions of apathy related to initiation or auto-activation (as opposed to emotion- or reward- driven aspects of apathy) (Passamonti et al., 2018). As Fig. 2 illustrates, reduced locus coeruleus activity can result from cell loss or increased inhibition. Various routes to this state help explain why apathy can manifest at different times in the disease course. While apathy occurs ubiquitously across manifest neuropsychiatric diseases of ageing, it also occurs in the earliest and even presymptomatic stages (Malpetti et al., 2021a). Locus coeruleus *hyperactivity* may contribute to an anxious or agitated phenotype. The locus coeruleus-noradrenergic system mediates an adaptive response to stress: stressful environmental stimuli provoke a high tonic mode of activity, shifting an organism towards sampling and scanning behaviours (Valentino and Van Bockstaele, 2008) – potentially useful responses to extricate from a stressful situation. However, to be locked into this hypervigilant mode via increased locus coeruleus activity would recapitulate those aspects of anxiety, and animal models show that high tonic modes are sufficient to induce anxiety behaviours (McCall et al., 2015). The possibility that locus coeruleus hyperactivity can occur in response to pathological processes from the earliest and prodromal stages (Fig. 2b), fits with the anxiety commonly observed in prodromal phases of Alzheimer's and Parkinson's disease (Gallagher et al., 2011; Postuma and Berg, 2019). The noradrenergic system is also closely linked with dimensions of impulsivity that involve inhibiting a response or cancelling an initiated action. Here the role of noradrenaline in reconfiguring large-scale networks may be especially apparent, as engagement of prefrontal-striatal networks appears key to successful inhibition (Dalley and Robbins, 2017; Rae et al., 2016; Ye et al., 2015).

Other aspects of cognition are affected by noradrenergic dysfunction

in diseases of ageing. Task engagement and selection driven by the locus coeruleus-noradrenergic system can prioritise and guide interactions with the environment – a function synonymous with attention (Hommel et al., 2019; O'Callaghan et al., 2021a). Novelty-induced locus coeruleus activity (and connectivity) is reduced in older people with amyloid-related cognitive decline – a prodromal phase of Alzheimer's disease – which explains diminished sensitivity to attend and adapt to environmental affordances (Prokopiou et al., 2022). A direct role for the locus coeruleus-noradrenaline system in memory is also apparent: noradrenergic modulation of hippocampal β-adrenergic receptors regulates synaptic plasticity and enhances encoding (Hagena et al., 2016). Also, the timing of locus coeruleus firing during non-REM sleep is nested within other oscillatory rhythms, supporting the consolidation and pruning of memories that occurs during sleep (Poe, 2017). Disruptions to these noradrenaline-mediated encoding and consolidation functions indicate a more direct role in memory impairment, over and above what might be secondary to attention problems. Integrity of the locus coeruleus-noradrenergic system has been extensively linked with memory performance in ageing and Alzheimer's disease (Dahl et al., 2022, 2019; Hämmerer et al., 2018; Jacobs et al., 2021). Furthermore, locus coeruleus-noradrenergic dysfunction is implicated in age-related cognitive decline – with integrity of this system proposed to be a determinant of cognitive/neural reserve (Mather and Harley, 2016; Robertson, 2013; Wilson et al., 2013).

Given that dysfunction in the noradrenergic system underlies behavioural and cognitive deficits, it is surprising that noradrenergic drugs are not more commonly used to treat symptoms. Existing noradrenergic compounds are available and licensed for other conditions. These include (i) relatively selective (e.g., atomoxetine) and less selective (e.g., methylphenidate) noradrenaline reuptake inhibitors, which increase extracellular availability of noradrenaline; and (ii) α2 agonists such as clonidine and the more selective α2A agonist guanfacine, which mimics noradrenaline's effects by stimulating the post-synaptic α2A receptor (Arnsten, 2020). Evidence from clinical trials using these repurposed drugs has varied. But rather than abandoning such endeavours, this variance highlights the need for better stratification in clinical trials so that likely responders can be identified (David et al., 2022). For example, encouraging results are seen with methylphenidate and other noradrenergic drugs for apathy in Alzheimer's disease (David et al., 2022; Mintzer et al., 2021), atomoxetine for treating cognition, impulsivity and markers of apathy in Parkinson's (Hezemans et al., 2022; Marsh et al., 2009; Weintraub et al., 2010), with further evidence for a neuroprotective effect of atomoxetine in mild cognitive impairment (Levey et al., 2022). The locus coeruleus is a key site for assessing the integrity of the noradrenergic system, and to identify who will respond best to treatment (O'Callaghan et al., 2021b). Recent advances in neuroimaging approaches mean that accurate in vivo measurement of the locus coeruleus in neuropsychiatric diseases of ageing is becoming increasingly accessible (Betts et al., 2019; Ye et al., 2021).

2.2. Cholinergic system

Much of the brain's cholinergic innervation arises from a small group of nuclei in the basal forebrain. These nuclei have stolen the spotlight in dementia research and treatment for decades. Since coining the "cholinergic hypothesis" (Bartus et al., 1982), many of the cognitive deficits in neuropsychiatric diseases of ageing have been viewed through a cholinergic lens. The most commonly used drugs to treat memory loss and hallucinations in Alzheimer's disease and Parkinson's disease dementia enhance cholinergic function. However, the understanding of the cholinergic system has undergone substantial revision and treatment options have not necessarily kept pace. As the prototypical cholinergic disorder, a relationship between cholinergic impairment and cognitive decline is long since observed in Alzheimer's disease (Bowen et al., 1976; Perry et al., 1978). Similar relationships are apparent in Parkinson's disease, where cholinergic dysfunction (or anticholinergic treatment of tremor) is associated with cognitive impairment and dementia (Dunois et al., 1983; Whitehouse et al., 1983). Cholinergic deficits are also well documented in Lewy body dementia (Perry et al., 1993) and progressive supranuclear palsy (Juncos et al., 1991).

Basal forebrain cholinergic neurons are interspersed among non-cholinergic neurons and interneurons (Ballinger et al., 2016; Zaborszky et al., 2015). Described as "open" nuclei, these cholinergic-containing cell groups overlap, rather than respecting strict anatomical boundaries (Liu et al., 2015; Mesulam et al., 1983). Order comes from the Ch1-Ch4 nomenclature, which designates the main cholinergic cell groups within basal forebrain nuclei (Mesulam et al., 1983; Mesulam and Geula, 1988). These include cholinergic cells in the medial septal nucleus (Ch1), the vertical limb of the diagonal band nucleus (Ch2), the horizontal limb of the diagonal band nucleus (Ch3) and the nucleus basalis of Meynert (Ch4). These cell groups provide cholinergic input to the hippocampal complex and thalamus (Ch1, Ch2), olfactory bulb (Ch3), cortex and amygdala (Ch4). Another cholinergic projection system arises from the brainstem, localised to the pedunculopontine nucleus (Ch5), the dorsolateral tegmental nucleus (Ch6), the medial habenular nucleus (Ch7) and the parabigeminal nucleus (Ch8). Their projection sites include the thalamus, hypothalamus, striatum and basal forebrain, as well as midbrain nuclei, the substantia nigra, interpeduncular nucleus and superior colliculus (Dautan et al., 2014; Hallanger and Wainer, 1988; Ren et al., 2011; Steriade et al., 1988). Aside from these projection systems, a third population of cholinergic interneurons serves a local function in the striatum. These striatal cholinergic interneurons are few in number, but they achieve dense innervation throughout the striatum via extensive arborisation (Bolam et al., 1984; Contant et al., 1996). They provide a major regulatory influence over the striatal complex: modulating medium spiny neurons (MSNs) and GABAergic interneurons, and triggering dopamine release (Koós and Tepper, 2002; Threlfell et al., 2012).

Cell loss in the cholinergic basal forebrain and degeneration of cortical cholinergic axons occurs early in Alzheimer's disease, from the prodromal stages (Mesulam et al., 2004). With the Ch4 population particularly vulnerable to pathological accumulation and degeneration. There is a similar predilection for the Ch4 population in Parkinson's disease, although the pattern of neuronal loss differs in the two conditions (Liu et al., 2015). Cholinergic deficits may be a distinctive feature of dementia in the context of Lewy body diseases – perhaps unsurprisingly, given that Parkinson's disease dementia and dementia with Lewy bodies share the same pathophysiology. These conditions are distinguished by dementia occurring in the context of well-established Parkinson's disease (Parkinson's disease dementia) and dementia occurring before or concurrent with parkinsonism (dementia with Lewy bodies) (Walker et al., 2015). Cholinergic deficits are more severe in Parkinson's disease dementia and dementia with Lewy bodies, compared to both Parkinson's disease and Alzheimer's disease (Bohnen et al., 2022; Francis and Perry, 2007). Parkinson's disease also sees deficits in cholinergic striatal interneurons and brainstem projection sites (notably the pedunculopontine nucleus) (Bohnen et al., 2022), with a similar pattern involving the basal forebrain, striatal and brainstem cholinergic systems seen in progressive supranuclear palsy (Warren et al., 2005). Early cholinergic compensatory responses have been observed in mild cognitive impairment, Alzheimer's disease, Parkinson's disease and Lewy body dementia – with increased activity, up-regulation of receptors and sprouting of cholinergic terminals (Craig et al., 2020; DeKosky et al., 2002; Mufson et al., 2015).

The action of acetylcholine is mediated through two families of receptors: G-protein coupled, metabotropic muscarinic acetylcholine receptors (mAChRs), and excitatory, ligand-gated, ionotropic nicotinic acetylcholine receptors (nAChRs). Both receptor types are found at pre- and post-synaptic sites, including on the pre-synaptic terminals of non-cholinergic neurons – this permits heterosynaptic influence, altering neuron excitability or release probability of other neurotransmitter systems (Thiele, 2013). In general, at pre-synaptic locations their

activation can modulate the release of many neurotransmitters (e.g., acetylcholine, dopamine, serotonin, noradrenaline, glutamate and GABA), post-synaptically they influence membrane potential, and at non-synaptic locations they influence the excitability and setpoints of neurons, determining their sensitivity and responsiveness (Dani and Bertrand, 2007).

Muscarinic receptors couple to $G_{q/11}$ (including M1, M3, M5 subtypes; known as M1-type) and $G_{i/o}$ (including M2, M4 subtypes; known as M2-type) families (Caulfield and Birdsall, 1998). These receptors cause a variety of second messenger cascades, primarily via activating phospholipase C (M1-type) and inactivating adenylyl cyclase (M2-type). The effects of muscarinic stimulation vary, dependent on receptor subtype and location. Post-synaptic mAChRs are excitatory (M1-type) or inhibitory (M2-type); pre-synaptic mAChRs are typically inhibitory, acting as autoreceptors on cholinergic terminals or heteroreceptors on non-cholinergic terminals, to curtail cholinergic activity and activity in other neurotransmitters (Picciotto et al., 2012; Thiele, 2013). Nicotinic ionotropic activation produces a faster response, in contrast to the slower, longer lasting effects of metabotropic muscarinic activation. A family of 12 nAChR subunits have been identified in the human brain (α2-α10 and β2-β4), with α4β2 and α7 being the most common (Ballinger et al., 2016; Zoli et al., 2015). Only a minority of nAChRs are expressed post-synaptically, with the majority in pre-synaptic or extra synaptic locations where they influence neurotransmitter release and neuron responsivity (Dani and Bertrand, 2007; Picciotto et al., 2012). The α7 receptors are relativity low affinity, producing a fast response with high calcium conductance and rapid desensitisation, in contrast to the higher affinity α4β2 receptors that have lower calcium conductance and slower desensitisation kinetics (Albuquerque et al., 2009; Dani and Bertrand, 2007). Broadly speaking, α7 stimulation promotes glutamate release and α4β2 promotes GABA release (Picciotto, 2003).

Cholinergic circuitry differs substantially across brain regions (Disney et al., 2006; Raghanti et al., 2008) and across species (Disney and Reynolds, 2014). While a canonical cholinergic circuit may not exist, similar computations occur across these systems (Coppola and Disney, 2018), which in the cortex and hippocampus support the simultaneous enhancement of afferent input and suppression of intrinsic activity (Hasselmo and Giocomo, 2006). Muscarinic M1 and M2 receptors are prominently expressed in the prefrontal cortex of humans, non-human primates and rodents (Vijayraghavan and Everling, 2021). In primate dorsolateral prefrontal cortex, M1 receptors are expressed in all cortical layers (with a predominance in layers III, V, VI) on pyramidal and interneuron dendritic shafts and pyramidal spines, primarily post-synaptically; M2 receptors are located on pyramidal dendritic spines and interneuron dendritic shafts, primarily pre-synaptically (Galvin et al., 2018; Medalla and Barbas, 2012; Mrzljak et al., 1993; Vijayraghavan and Everling, 2021). In the primate dorsolateral prefrontal cortex, α7 receptors are highly expressed in layer III, positioned in the post-synaptic density of dendritic spines (Yang et al., 2013). α4β2 receptors are also highly expressed in the primate prefrontal cortex (Quik et al., 2000), which in the rodent prefrontal cortex have been localised to interneurons and layer VI pyramidal cells (Bloem et al., 2014).

Muscarinic receptor distribution in the primate prefrontal cortex supports enhancement of thalamocortical and corticocortical excitatory transmission via post-synaptic M1 receptors and suppressive effects via pre-synaptic M2 receptors (Medalla and Barbas, 2012; Vijayraghavan and Everling, 2021). Enhancement of thalamocortical input via nicotinic receptors has been shown extensively in the rodent prefrontal cortex (Poorthuis et al., 2009). Moreover, in the primate dorsolateral prefrontal cortex cholinergic circuitry plays a unique role in higher-order cognitive function. Here acetylcholine is critical for persistent pyramidal cell firing, which relies on glutamatergic transmission at NMDA receptors (in particular those with the GluN2B subunit) located in the post-synaptic density of excitatory synapses on layer III spines (Wang et al., 2013). Slow kinetics of the NMDA receptor and GluN2B subunit are ideal for supporting persistent firing of layer III pyramidal delay cells – which maintain excitation in the absence of sensory stimuli to keep information "in mind", providing the foundation for complex and temporally protracted cognitive operations (Goldman-Rakic, 1995). Acetylcholine plays a permissive role in this circuitry (See Fig. 1b). Simulation of nicotinic α7 receptors in the post-synaptic density of glutamatergic synapses on dendritic spines directly depolarises the post-synaptic membrane to permit NMDA receptor activation (Yang et al., 2013), with M1 stimulation contributing indirectly to membrane depolarisation by closing K+ channels in the post-synaptic density (Galvin et al., 2020).

Evidence from the rodent hippocampus shows that muscarinic signalling modulates synaptic plasticity (Teles-Grilo Ruivo and Mellor, 2013), via M1 activation in CA1 that enhances NMDA receptor responses to promote long-term potentiation (Drever et al., 2011; Markram and Segal, 1992). With activation of muscarinic receptors in the entorhinal cortex modulating persistent firing activity (Egorov et al., 2002) and spatial tuning of grid cells (Newman et al., 2014) – further supporting a key role for acetylcholine in plasticity in the rodent hippocampus. Nicotinic mechanisms of plasticity are also evident from rodent hippocampus, with α7 among the most abundant and are expressed on most neuron types. They contribute to synaptic plasticity through a number of mechanisms (Letsinger et al., 2022; Teles-Grilo Ruivo and Mellor, 2013), and based on the timing of their activation relative to glutamate transmission, will promote either long-term potentiation or short-term depression (Gu and Yakel, 2011).

In the striatum, M1 receptors are expressed on both D1-MSNs of the direct and D2-MSNs of the indirect pathways, with M4 receptors also on the D1-MSNs (Mamaligas et al., 2019). Functional consequences of muscarinic stimulation have been described in the rodent striatum (Ding et al., 2010). Striatal cholinergic interneurons display tonic pacemaker activity, which shifts to a burst-pause firing mode primarily via excitatory input from thalamic intralaminar neurons. This reconfiguration of cholinergic release causes transient suppression of cortical input to both classes of MSNs, followed by enhancement of indirect pathway MSNs, together permitting interruption of an ongoing behaviour (Ding et al., 2010). Unlike muscarinic receptors, in the striatum nAChRs are not expressed on MSNs but they are found on most classes of striatal interneurons (Assous, 2021). As shown in rodents, they modulate MSNs indirectly, via GABAergic inhibition from interneurons. As GABAergic interneurons provide the main source of feedforward inhibition over MSNs, activation of nAChRs provides a "brake" on MSN responsiveness to cortical input. In response to phasic activation this supports the interruption of ongoing behaviour (English et al., 2012), whereas tonic nAChR activation contributes to increased basal GABAergic tone that curtails striatal output over a longer timescale (Matityahu et al., 2022).

2.2.1. *A spectrum of spatiotemporal precision*

The widespread nature of cholinergic projections (Fig. 1b) and overlapping dendritic fields of basal forebrain cholinergic cells, might suggest a diffuse system lacking in spatial and functional precision (Saper, 1987; Woolf, 1991). However, basal forebrain neurons display patterns of both overlap and segregation. Within basal forebrain cholinergic cell groups, neurons are segregated along anterior-posterior, ventral-dorsal and medial-lateral axes that correspond to functionally specific target locations (Ballinger et al., 2016; Kim et al., 2016). The extent to which these neurons are segregated vs. overlapping relates to the location of their cortical targets: highly interconnected cortical targets are innervated by overlapping basal forebrain cholinergic cells, and disparate targets are innervated by segregated bands of cholinergic neurons (Zaborszky et al., 2015). These findings recast the cholinergic system from a purely *mosaic* organisation of overlapping cell groups projecting to overlapping target regions, to one that also exhibits a highly *modular* organisation capable of modulating cognition according to precise expressions of functional anatomy (Muñoz and Rudy, 2014; Turchi et al., 2018).

The precision of cholinergic signalling is also achieved via wired

transmission (Sarter et al., 2009). Wired transmission entails fast (millisecond to second), spatially precise, one-to-one signalling between pre- and post-synaptic sites. This is typically associated with ionotropic neurotransmitters (e.g., glutamate, GABA) and contrasted against the volume transmission of neuromodulators (Fig. 3). A key question here is whether or not cholinergic axons make synapses? Evidence is mixed, with reports of synaptic incidence for cholinergic varicosities varying widely between 7% and 76% (Disney and Higley, 2020; Muller et al., 2013; Umbriaco et al., 1994). The presence of high-affinity cholinergic receptors in the extra-synaptic space (Jones and Wonnacott, 2004; Mrzljak et al., 1993) supports a role for volume transmission, where ambient levels of acetylcholine diffuse to exert prolonged regulatory effects (Descarries et al., 1997; Descarries and Mechawar, 2000). Ambient acetylcholine is well documented using microdialysis, although the spatial and temporal limitations of this technique restrict it to measuring extracellular levels over the course of minutes (Sarter and Lustig, 2020). In this way, interpretations based on microdialysis are biased to detect volume transmission. Newer technologies have increased temporal resolution and the ability to measure at the synaptic cleft, uncovering more diverse spatiotemporal scales (Parikh et al., 2004). In favour of wired transmission is the extraordinary catalytic power of acetylcholinesterase, which acts among the fastest of any enzyme to hydrolyse ~5000 molecules of acetylcholine per second (Acheson and Quinn, 1990; Shen et al., 2002). Such efficiency would severely limit the opportunity for spill-over into extra-synaptic space (Sarter et al., 2009); for volume transmission to occur, mechanisms that tightly regulate expression of acetylcholinesterase would be needed (Disney and Higley, 2020).

Both fast (synaptic) and slow (extra-synaptic) cholinergic signalling may occur – mapping onto both phasic and tonic firing patterns in support of different brain states and behaviours. Indeed, the recognition of phasic or "transient" activation, alongside extra-synaptic modulatory effects, mirrors the dynamic properties of the noradrenergic system (Sarter et al., 2016). Rapid cholinergic spikes occur within 500 msec of a behavioural stimulus, while optogenetic stimulation reveals cholinergic signalling in the range of 10–100 msec (Gritton et al., 2016; Nelson and Mooney, 2016). These transients are robustly linked to cue detection (Parikh et al., 2007). Distinct cholinergic cell populations in the basal forebrain that show early (more excitable) versus later (less excitable) firing are candidates for mediating these separate phasic and tonic patterns (Unal et al., 2012). An additional factor in cholinergic transmission is the distinction between rhythmic and burst patterns of firing by basal forebrain cholinergic cells. These may both contribute to the phasic response to a salient event (via single spikes or burst firing, respectively), but with distinct functional consequences (Laszlovszky et al., 2020). The nature of striatal cholinergic interneuron transmission is less understood, it is likely that a combination of ambient (tonic) and discrete time-resolved (phasic) transmission occurs (Nosaka and Wickens, 2022), enabling multiple modes of cholinergic operations in the striatum.

2.2.2. *Cholinergic neuropsychiatric symptoms*

Many medications have anticholinergic properties, either as their intended mode of action (e.g., smooth muscle relaxation to alleviate bladder and bowel symptoms; or relief of nausea), or as side effects (e.g., neuroleptics, diuretics, antihistamines, diuretics, tricyclic antidepressants). These anticholinergic effects can cause confusion, delirium and chronic cognitive impairment sufficient to mimic dementia, or to severely exacerbate cognitive disorders. Sedation is common, and hallucinations may occur. This mimicry of neuropsychiatric symptoms highlights the role of the cholinergic system in neuropsychiatric disorders, and suggests cholinergic strategies to alleviate symptoms. However, just as anticholinergic side effects often lack specificity, it has been difficult to harness cholinergic treatments with sufficient specificity to

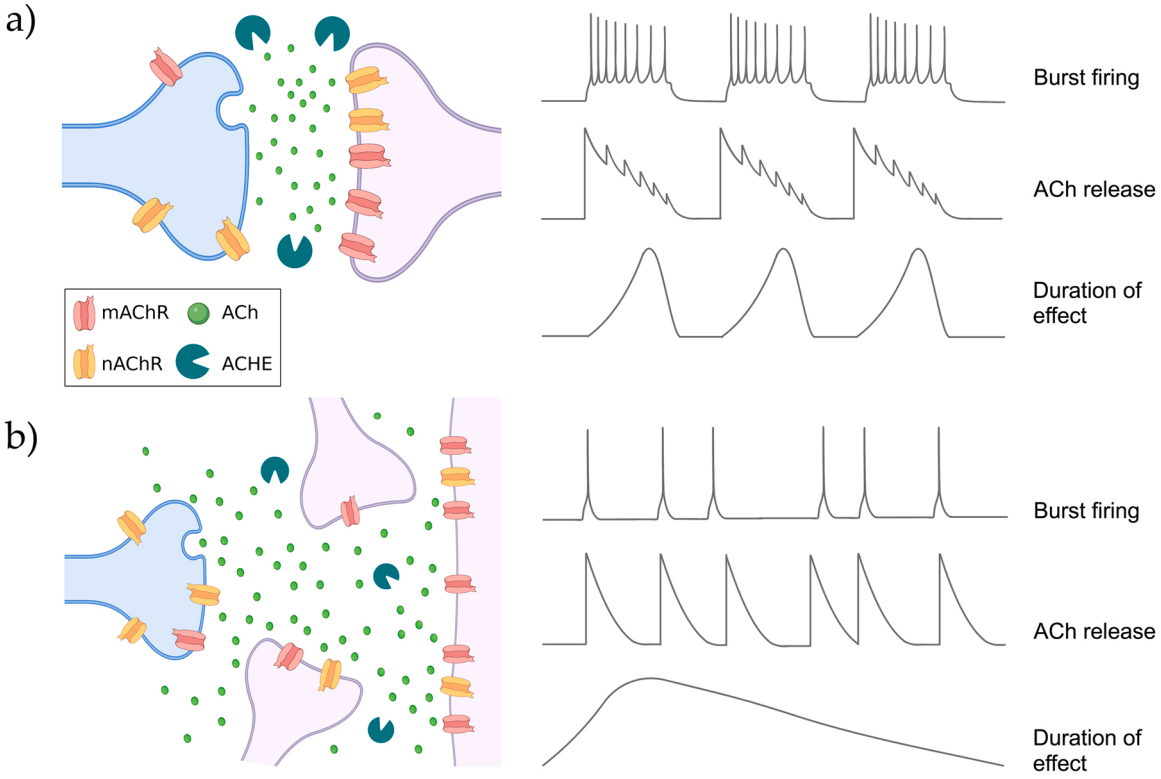

Fig. 3. Acetylcholine (ACh) transmission and release patterns **a) Wired transmission**, where ACh release is confined to the synaptic cleft and quickly taken up by acetylcholinesterase. This may be associated with burst firing patterns, where ACh is released in a temporally specific manner for limited duration; **b) Volume transmission,** where ACh escapes the synaptic cleft and stimulates non-junctional receptors. This may be associated with tonic firing patterns and a temporally extended effect.

target symptoms for individual benefit.

Similar to noradrenaline, early theories of cholinergic function centred on a non-specific role in arousal or cortical excitability. Yet the early associations with cognitive decline in dementia, and pharmacological experimental literature, suggested roles in learning, memory and attention. An early overarching theory of cholinergic function – which captured emerging ideas about its electrophysiology and behavioural correlates – was that it boosts signal-to-noise ratios in target regions (Everitt and Robbins, 1997). Later computational accounts continued to emphasise a role in controlling neuronal noise – e.g., by promoting divisive normalisation (Schmitz and Duncan, 2018). At the level of neuronal populations, this reflects a "desynchronised" or high-conductance state where spontaneous neuronal fluctuations are weaker (Destexhe et al., 2003; Harris and Thiele, 2011), and there is enhanced sensory processing and increased task engagement (Beaman et al., 2017; McGinley et al., 2015). Acetylcholine modulates signal-to-noise relationships both at the individual cortical neuron level (Zinke et al., 2006) and the population level (Minces et al., 2017). As a result, a characteristic of cholinergic innervation is the enhancement of afferent (external) pathways and suppression of recurrent (internal) pathways (Giocomo and Hasselmo, 2007), leading to specificity of sensory processing, encoding and plasticity. These effects unfold over multiple timescales, with phasic transients promoting cue-directed behaviour (i.e., where a salient environmental cue might prompt a shift from an ongoing task), and a slower modulatory component associated with stabilising ongoing behaviour and resisting distraction (Sarter and Lustig, 2019).

The cholinergic system is therefore able to simultaneously enhance feedforward information flow and reduce the influence of lateral intracortical connections. This has been conceptualised as a filtering process, where behaviourally relevant signals are processed and weak, irrelevant signals are filtered out (Sarter et al., 2005; Thiele, 2013). More specifically, cortical activation produced by a phasic signal sees an initial inhibition of layer V pyramidal neurons, followed by action potential generation in layers II/III and V (Gulledge et al., 2009). Transient inhibition, with longer-lasting excitability, may provide a necessary window to "reset" layer V neurons so that subsequent activity reflects newly updated patterns of afferent input (Gulledge et al., 2009; Thiele, 2013), perhaps setting the stage for the mAChR-activated persistent firing patterns associated with maintenance of sensory input (i.e., working memory) (Croxson et al., 2011; Hasselmo and Sarter, 2011). Disruption of these cortical processes by anticholinergic drugs may underlie their induction of hallucinations and reduction of attention and learning.

A role in integrating new, cue-driven patterns into ongoing behaviour is also mirrored at the level of the striatum. Following a salient stimulus, thalamic drive over cholinergic interneurons leads to suppression of both indirect and direct pathways, followed by prolonged enhancement of the indirect pathway (Ding et al., 2010). This interrupts and suppresses now-unwanted behavioural programs, providing a substrate for reconfiguring behavioural output (Ding et al., 2010; Goldberg et al., 2012; Thorn and Graybiel, 2010).

Clearly disruptions to the cholinergic system will have pervasive consequences for neuropsychiatric diseases of ageing. In Alzheimer's and Parkinson's disease, and the associated dementia with Lewy bodies and Parkinson's disease dementia, measures of cholinergic dysfunction, both in vivo and *post mortem*, have been related to overall cognitive impairment (Barrett et al., 2019; Grothe et al., 2010, 2021; Hall et al., 2014; Mesulam et al., 2004). In Parkinson's disease, cholinergic dysfunction correlates with cognitive decline independent from dopaminergic loss (Bohnen et al., 2012). Cholinergic dysfunction is related to deficits in sensory processing, learning, memory and attention, which have in common the need for precision in signal detection, enhancing relevant information processing and encoding (Hasselmo, 1999). Short-term memory is impacted given the key role of cholinergic processes in both hippocampal (Drever et al., 2011) and cortical (Rasmusson, 2000) synaptic plasticity. Anxiety and depression are linked with elevated cholinergic activity (Dulawa and Janowsky, 2019), through both nicotinic (Picciotto et al., 2015) and muscarinic (Drevets et al., 2013) signalling. Up-regulation of the cholinergic system in the earliest disease stages may also influence some of the prodromal features of anxiety and depression observed in Alzheimer's and Parkinson's disease.

A clear difference between cholinergic and noradrenergic systems is apparent in the association with psychosis and delirium, particularly visual hallucinations. Visual hallucinations in older adults have a long-held association with the cholinergic system, e.g., muscarinic antagonism can cause visual hallucinations (Perry et al., 1999). This fits with the dual role of cholinergic signalling in amplifying thalamic inputs and weakening intra-cortical feedback. If imbalanced, this circuitry may simultaneously impair processing of sensory input and permit intrusions from internally generated information – processes that underpin mechanistic frameworks for visual hallucinations in neuropsychiatric diseases of ageing (Collerton et al., 2005; O'Callaghan et al., 2017; Shine et al., 2014). In Lewy body dementia and Parkinson's disease reduced cholinergic function has also been associated with visual hallucinations (Hepp et al., 2013; Manganelli et al., 2009; Teaktong et al., 2005).

Cholinergic therapeutics are now in common clinical practice. Cholinesterase inhibitors (e.g., rivastigmine, galantamine and donepezil), inhibit the breakdown of acetylcholine leaving more available in the synaptic cleft. They are approved treatments for cognitive symptoms in Alzheimer's disease. Evidence also supports their use in Parkinson's disease and Lewy body dementia (Walker et al., 2015), particularly in the suppression of hallucinations and to some extent cognitive improvement. They can worsen cognition and agitation in frontotemporal dementia, which does not cause a severe cholinergic deficit (Murley and Rowe, 2018). Cholinesterase inhibitors can improve a range of clinical features, including cognition, visual hallucinations (O'Brien et al., 2020) and depression/anxiety (Cummings et al., 2016). However, the cognitive improvements are typically modest, and while significant at a group level the benefits may not be discernible in all individuals. This should not be interpreted as a lack of benefit, as slower decline is better than faster decline. Efficacy and responsiveness could potentially be enhanced with earlier intervention and higher doses (Giacobini et al., 2022). However, the group-wise benefits of treatment over placebo or withdrawal persist even into advanced stages of dementia; while there is inconclusive evidence that cholinesterase inhibitors help in the earliest (prodromal) mild cognitive impairment stage (Matsunaga et al., 2019; Stage et al., 2021). The risk of central and peripheral side-effects is higher at higher doses, and while cholinesterase inhibitors boost basal levels of acetylcholine, this may obscure cholinergic transients and reduce the dynamic range of the system (Dumas and Newhouse, 2011). Taken together, the overall modest benefits of cholinesterase inhibitors, and their lack of specificity, suggest the need for alternatives to target cholinergic deficits in dementia and parkinsonian disorders.

Targeting the cholinergic system in a receptor-specific manner is not trivial. Direct agonism still carries the risk of peripheral side effects and targeting select receptors is challenging because orthosteric binding sites are highly conserved across muscarinic and nicotinic receptor subtypes (Bouzat et al., 2018; Erskine et al., 2019). Recent decades have seen substantial efforts to develop muscarinic M1/M4 agonists (e.g., xanomeline), as well as nicotinic $\alpha4\beta2$ and $\alpha7$ agonists (Bouzat et al., 2018; Felder et al., 2018; Grupe et al., 2015; Moran et al., 2019). These have met with limited clinical success, as cognitive benefits have come with peripheral side effects. Positive allosteric modulators (PAMs) have emerged as a more promising contender. Compared to agonists, positive allosteric modulators show higher selectivity as allosteric sites are less conserved, they have low intrinsic activity and can better preserve spatiotemporal characteristics of endogenous acetylcholine activation, as they only act when it is present (Bouzat et al., 2018). Reliance on endogenous acetylcholine availability presents a caveat for

neurodegenerative diseases, which might limit the efficacy of positive allosteric modulators to less severe disease stages when endogenous levels are better maintained (Erskine et al., 2019). Notwithstanding, they retain promise as a novel treatment, which may help preserve the spatiotemporal fidelity of cholinergic signalling. A further caveat is that like noradrenaline, acetylcholine induced responses follow an inverted-U pattern in the primate prefrontal cortex. Low dose M1 receptor stimulation enhances task-related firing, but at higher doses firing is suppressed and cognition impaired (Galvin et al., 2020; Major et al., 2018; Vijayraghavan et al., 2018). While the mechanism underpinning this is unclear (perhaps driven by an M1-mediated excess in cAMP signalling (Galvin et al., 2020)), given that M1 receptor overstimulation can trigger neuronal suppression and have detrimental effects on cognition, efficacious dosing will remain an important challenge for M1-selective therapies (Vijayraghavan and Everling, 2021).

2.3. Interacting versus independent systems

Our discussion so far has considered the noradrenergic and cholinergic systems acting in isolation. There are distinctions between them. For example, noradrenergic fibres collateralise extensively, compared to the more targeted innervation of cholinergic fibres (Loughlin et al., 1982; Walker et al., 1985). They also differ in their respective input-output organisation. The basal forebrain has a relatively separable organisation, where its cell groups receive selective input from their projection regions (Gielow and Zaborszky, 2017). Whereas locus coeruleus neurons receive convergent input from many regions, and in turn project to diverse regions (Schwarz et al., 2015). Juxtaposed, this implies a greater capacity for the cholinergic system to support segregated processes, and for the noradrenergic system to support brain-wide integrative process (Rho et al., 2018; Shine, 2019). Another difference is their effect on the thalamic reticular nucleus, which is depolarised by noradrenaline but hyperpolarised by acetylcholine. Sitting interposed between the dorsal thalamus and cortex, the thalamic reticular nucleus regulates thalamocortical communication to enhance processing of salient information (Zikopoulos and Barbas, 2007). Through actions at the thalamic reticular nucleus, noradrenaline decreases spontaneous firing in the thalamus and acetylcholine increases it. So while they both enhance thalamic information processing, noradrenaline may drive a mode that is suited to more finely tuned discrimination and detection (Hirata et al., 2006). An advantage of these differences is to provide stabilisation, by introducing opponency that helps constrain a network to remain within an optimal range – preventing the "overmodulation" that could occur as such powerful neuromodulators converge on the same circuits (Disney, 2021; Marder, 2012).

However, there are interactions between them. They are richly interconnected and influence each other at every level of the processing hierarchy (Disney, 2021). This is characteristic of neuromodulators: they are not recruited separately (Briand et al., 2007), rather our thoughts and behaviours are shaped by a cocktail of neuromodulators exerting their effects in tandem (Brezina, 2010). For psychopharmacological treatments, drugs aimed at one system will often affect others.

Direct interactions arise from the unidirectional projection from the noradrenergic locus coeruleus to the basal forebrain (España and Berridge, 2006). There, cholinergic neurons are excited via α_1 and β_1 adrenoreceptors, and GABAergic neurons are inhibited via α_2 adrenoreceptors. This permits locus coeruleus activation to have an arousal-promoting effect over the basal forebrain (Jones, 2004; Schwarz and Luo, 2015). Cholinergic and noradrenergic systems also interact at the level of the thalamus, where they modulate cortical state (Hirata and Castro-Alamancos, 2010) and thalamocortical interactions (Hirata et al., 2006). Cholinergic and noradrenergic effects on thalamic firing patterns differ (McCormick, 1992; Varela, 2014), but both shift firing from rhythmic bursting into a tonic mode, optimal for information transmission to support ongoing cognitive operations (Goard and Dan, 2009; Rodenkirch et al., 2019). These systems also interact at the level of the cortex. For example, via reciprocal connections with the prefrontal cortex. Noradrenergic and cholinergic input has different effects on prefrontal cortex projection neurons, which in turn, influences the glutamatergic outputs that target the locus coeruleus and basal forebrain (Dembrow and Johnston, 2014). At the cortical microcircuit level they influence each other via heteroreceptors at axonal interaction sites, where noradrenaline can inhibit acetylcholine release (Vizi et al., 2010).

Few empirical studies have directly explored the behavioural consequences of noradrenergic and cholinergic interactions. Early work noted additive effects on memory impairment when both cholinergic and noradrenergic function were depleted (Haroutunian et al., 1990; Sahgal et al., 1990). More profound memory impairments with cholinergic depletion gave rise to the idea that noradrenaline's role in memory is at least partly due to its ability to enhance cholinergic activity (Dalmaz et al., 1993). At the level of the basolateral amygdala, both cholinergic and noradrenergic modulation contributes to the behavioural stress response. However, actions at the β2 nAChR sub-unit regulate efficiency of noradrenergic signalling within the basolateral amygdala – impacting its ability to influence the stress response, consistent with the idea that cholinergic activity alters the threshold for noradrenergic modulation of the basolateral amygdala (Mineur et al., 2018). Theoretical accounts converge on complementary roles for these systems in learning and probabilistic decision making. Acetylcholine may signal expected uncertainties based on predicted variability within the environment, whereas noradrenaline may signal unexpected uncertainties, i.e., when there is an abrupt, salient change within the environment (Parr and Friston, 2017; Yu and Dayan, 2005). Behaviourally, acetylcholine is linked to a learning rate that reflects how quickly existing memory is updated by new experience, and noradrenaline to a temperature parameter reflecting whether actions are explorative or stable (Doya, 2002). To better understand the functional consequences of these interacting systems, more comparisons using the same models and techniques are sorely needed.

The benefits of such interactions are clear. They expand the range of computations that could be performed by a system alone, and provide multiple avenues for resilience (Brezina, 2010). However, these interactions pose a challenge for understanding and treating neuropsychiatric disease. The implication is that pathology in one system affects the other – both by stimulating compensatory responses and by influencing further deterioration. Likewise, drugs aimed at modulating activity in one system will affect the other. For example cholinesterase inhibitors can increase or decrease noradrenaline levels depending on the dose (Giacobini et al., 1996; Trabace et al., 2000), while atomoxetine can enhance cortical acetylcholine release (Tzavara et al., 2006). We have not focused on other neuromodulatory systems – namely dopaminergic and serotonergic – also implicated in neuropsychiatric diseases of ageing. These neuromodulators share extensive bidirectional interactions with the cholinergic and noradrenergic systems, and they themselves undergo similar dynamic and variable changes across the disease course (Murley and Rowe, 2018; Pagano and Politis, 2018; Šimić et al., 2017). The use of serotonergic drugs for cognitive and psychiatric symptoms (e.g., SSRIs, pimavanserin) and dopaminergic drugs primarily targeting motor symptoms, poses a further challenge given their potential to interact with cholinergic and noradrenergic agents. Appreciation of the interactions, not only between cholinergic and noradrenergic systems but across the multitude of neurotransmitters acting in concert, will reveal further insights into the causes and treatments of neuropsychiatric symptoms.

3. New treatments of neuropsychiatric symptoms?

3.1. Personalised medicine to address non-linear effects and compensatory processes

We have highlighted the non-linearities of the locus coeruleus-noradrenaline system in terms of the inverted U-shaped dose-response

relationship (see Fig. 2), and compensatory responses. Compensatory responses can occur at the local level, for example, increasing activity within a region. Compensatory responses are also observed at the large-scale brain network level. In several neuropsychiatric diseases of later life, fMRI has shown increased connectivity related to preserved behavioural performance, suggestive of compensation (Franzmeier et al., 2018; O'Callaghan et al., 2016; Tsvetanov et al., 2021). However, mere increased connectivity may be less important than the dynamic organisation of connectivity. Network organisation is affected by neurodegenerative disease, as richly connected hub regions – critical for optimal information flow – are particularly vulnerable (Rittman et al., 2016; Stam, 2014). Preserving topological organisation may be a key factor in maintaining brain and behaviour resilience in the face of underlying pathology (Rittman et al., 2019), with measures of network topology linked to preserved performance in Alzheimer's and Parkinson's disease (Ewers et al., 2021; Shine et al., 2019). Certain symptoms may also be associated with regionally specific changes in network dynamics. For example, hallucinations in Parkinson's disease are associated with aberrant connectivity in large scale networks for sensory information processing and perception (Walpola et al., 2020; Yao et al., 2014); and non-linear interactions between prefrontal cortical projections to the subthalamic nucleus are associated with impulsivity, under noradrenergic regulation (Rae et al., 2016).

This approach poses the question, how might the initial conditions of a complex system constrain its trajectory? Complex systems do not forget their initial conditions: they "carry their history on their backs" (Juarrero, 2000). For disease states, this approach aims to explain how underlying pathology and existing resilience might influence the dynamic profile and trajectory of neuropsychiatric symptoms (Medaglia et al., 2017).

Such non-linear and baseline-dependent trajectories emphasise the need for personalised medicine that incorporates predictive models to determine individual responses to therapy. One approach to personalised medicine is to formalise *baseline dependency*: individual responses to drugs will depend on the baseline state of the system. For cholinergic and monoaminergic drugs, this dependency is well documented experimentally (Cools and D'Esposito, 2011; Rowe et al., 2008), but it is not routinely factored into clinical trials or general practice. Neuroimaging techniques that measure individual differences in neuromodulatory systems may bridge this gap (Cope et al., 2021; David and Malhotra, 2022). For example, diffusion-weighted imaging predicts response to monoaminergic drugs in Parkinson's disease (Ye et al., 2016), and locus coeruleus integrity correlates with the behavioural response to noradrenergic reuptake inhibition by atomoxetine (Hezemans et al., 2022; O'Callaghan et al., 2021b). Similarly, baseline acetylcholine activity and muscarinic receptor integrity predict response to cholinesterase inhibitors in Alzheimer's and Lewy body dementia (Colloby et al., 2020; Richter et al., 2018).

To measure the baseline state by imaging the neuromodulatory nuclei is challenging, given their small size and position deep within the brain. However, recent advances in structural and neurochemical imaging, together with brain atlases developed for diseases of ageing, are supporting this targeted imaging (Betts et al., 2019; Bohnen et al., 2018; Tiepolt et al., 2022; Ye et al., 2021). As we continue to reconcile neuromodulatory microcircuitry with large-scale brain dynamics and behaviour (Shine et al., 2021), dynamical systems approaches that capture nuanced features of brain organisation may also emerge as useful markers – particularly for subtle, prodromal compensatory changes. Together these tools offer a means of stratifying patients for clinical trials to maximise the potential to detect a response, and ultimately, to support personalised medicine.

3.2. Treatments that embrace the multiscale nature of these systems

The cholinergic system operates with temporal and spatial specificity, in addition to having a classic neuromodulatory influence. A picture emerges of a multiscale system that operates across time-scales and transmission modes, to meet specific behavioural challenges (Disney and Higley, 2020; Sarter et al., 2016, 2009). Operating over multiple timescales is a feature of both monoaminergic and cholinergic neuromodulatory systems. Their capacity for flexible signalling modes, their ability to broadcast both widespread and precise signals, and their diversity of receptors, equip them to operate at varying timescales to both rapidly initiate and stabilise ongoing behaviour (Grossman and Cohen, 2022).

Drug treatments that better preserve spatiotemporal characteristics of these endogenous systems are an important goal, although not easily achievable. Compared to the non-specific effects of cholinesterase inhibitors, positive allosteric modulators might agonise this system in a receptor-specific manner to mimic endogenous activity. Similar concerns arise for noradrenergic treatments. Noradrenergic drugs (i.e., atomoxetine, guanfacine) are currently being repurposed for neuropsychiatric diseases of ageing (i.e., Alzheimer's disease, Parkinson's disease), to enhance cortical synaptic efficiency, even if they may also reduce phasic firing via autoreceptor actions at the locus coeruleus (Chernoff et al., 2021). The resulting shift towards a higher tonic state and dampening of phasic patterns can enhance adaptive behavioural flexibility, but may impair other aspects of cognition – a trade-off that needs continued investigation.

Greater appreciation of the multiscale nature of these systems will shape emerging stimulation therapies. For example, low frequency (20 Hz) deep brain stimulation of the nucleus basalis of Meynert has phase I evidence of being safe and well tolerated in mild-moderate Alzheimer's disease (Kuhn et al., 2015) and Parkinson's disease dementia (Gratwicke et al., 2018). Importantly, continuous stimulation of nucleus basalis of Meynert in rodent and monkey models has no effect or even degrades performance, whereas intermittent stimulation leads to cognitive improvements (Blake et al., 2017; Koulousakis et al., 2020; Liu et al., 2017). This suggests basal forebrain stimulation will need a different approach to the continuous, high frequency stimulation typically used in Parkinson's disease. Those parameters quell output from a target region to achieve their therapeutic effects, whereas non-traditional low frequency/intermittent patterns may enhance local activity, which in the basal forebrain would promote acetylcholine release (Subramaniam et al., 2021).

3.3. From symptom mitigation to neuroprotection?

Restoring noradrenergic and cholinergic function has mainly been used to mitigate symptoms, but there is the possibility of a neuroprotective effect. Noradrenergic and cholinergic signalling also regulates neuroinflammatory responses. These systems toggle different arms of the inflammatory pathway, with adrenergic receptors expressed on microglia and astrocytes influencing the pro-inflammatory response, and cholinergic receptors on microglia influencing the anti-inflammatory response (Carnevale et al., 2007). The degree of inflammation is related to disease severity and rate of decline in Alzheimer's disease and other dementias (Malpetti et al., 2021b, 2020).

In rodent models of Alzheimer's disease, depleted noradrenaline is associated with uncontrolled inflammation, along with impaired microglial migration and phagocytosis that reduces amyloid-β clearance (Flores-Aguilar et al., 2022; Heneka et al., 2010). This is complemented by rodent studies showing that β-adrenergic agonists have protective effects on microglia action and can enhance neurogenesis (Chai et al., 2016; O'Neill et al., 2020; Xu et al., 2018). Encouragingly, the possibility of noradrenaline-mediated neuroprotective effects was recently observed in humans. In a phase II trial of mild cognitive impairment patients, atomoxetine was associated with reduced CSF tau, changes in inflammation and glial markers, and, increased brain-derived neurotrophic factor (Levey et al., 2022). At the earlier stages, a potential role for noradrenergic agents in reducing the risk of Alzheimer's disease is possible. Excessive cAMP-calcium signalling has been shown to drive tau

phosphorylation in the dorsolateral prefrontal cortex of ageing non-human primates (Datta et al., 2021) and is proposed as a predisposing risk factor for Alzheimer's disease (Arnsten et al., 2021). High noradrenaline levels, for example during stress, drive feedforward cAMP-calcium signalling (Arnsten, 2015), raising the possibility that regulating noradrenergic activity earlier in life may reduce the risk of Alzheimer's disease. A body of preliminary evidence links cholinesterase inhibitors in Alzheimer's disease to a stabilisation of disease progression, associated with reduced rates of brain atrophy (Hampel et al., 2019). This is paralleled by Alzheimer's rodent models showing that M1 agonists can influence inflammation, amyloid-β clearance and tau phosphorylation (Giacobini et al., 2022). In combination with exploring new cholinergic and noradrenergic therapies, looking at markers of disease progression will be important. The possibility that these drugs could have positive effects on disease progression will also inform their use in the clinic.

4. Conclusion

Noradrenergic and cholinergic systems have a powerful influence over brain states and behaviour. The early theories focussed on arousal, the sleep wake cycle and cortical excitability (Hobson et al., 1975; Moruzzi and Magoun, 1949). Later works have extended and nuanced the theoretical framework to understand noradrenergic and cholinergic systems in health and disease, and their non-linear regulation of behaviour and cognition. These normative accounts help to understand the impact of noradrenergic and cholinergic deficits in diverse neuropsychiatric diseases associated with ageing. They also point the way forward to new symptomatic treatments, within a personalised medicine framework.

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