Neurobiologic Rationale for Treatment of Apathy in Alzheimer’s Disease With Methylphenidate

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Abstract

The public health burden of Alzheimer’s disease (AD) is related not only to cognitive symptoms, but also to neuropsychiatric symptoms, including apathy. Apathy is defined as a quantitative reduction of goal-directed activity in comparison to a previous level of functioning and affects 30%–70% of persons with AD. Previous attempts to treat apathy in AD—both nonpharmacologically and pharmacologically—have been wanting. Catecholaminergic treatment with methylphenidate has shown encouraging results in initial trials of apathy in AD. Understanding the neuronal circuits underlying motivated behavior and their reliance on catecholamine actions helps provide a rationale for methylphenidate actions in the treatment of apathy in patients with AD. Anatomical, physiological, and behavioral studies have identified parallel, cortical-basal ganglia circuits that govern action, cognition, and emotion and play key roles in motivated behavior. Understanding the distinct contributions to motivated behavior of subregions of the prefrontal cortex—dorsolateral, orbital-ventromedial, and dorsomedial—helps to explain why degeneration of these areas in AD results in apathetic behaviors. We propose that the degeneration of the prefrontal cortex in AD produces symptoms of apathy. We further propose that methylphenidate treatment may ameliorate those symptoms by boosting norepinephrine and dopamine actions in prefrontal-striatal-thalamocortical circuits.

Keywords

Alzheimer’s disease; apathy; methylphenidate; prefrontal cortex; catecholamines; norepinephrine; dopamine

INTRODUCTION

The public health burden of Alzheimer’s disease (AD) is related not only to cognitive symptoms, but also to neuropsychiatric symptoms. Most patients with AD will develop at least one such symptom over the course of the disease. Common neuropsychiatric symptoms in AD include agitation, depression, and apathy. Apathy is defined as a quantitative reduction of goal-directed activity in comparison to a previous level of functioning and affects 30%–70% of persons with AD. Even in the prodromal condition of mild cognitive impairment, apathy has an estimated prevalence of 15%–18% and is associated with a significantly increased risk of incident dementia. Numerous studies have shown that apathy is among the neuropsychiatric symptoms most associated with caregiver time and distress. Thus, apathy adds to the public health burden of AD, particularly for caregivers, and is an important target for treatment.

Previous efforts to treat apathy in AD have left a large unmet need. Nonpharmacologic interventions would be preferred as first-line interventions if effective, because they are lower risk than pharmacologic interventions. Interventions to engage the patient in recreational and social activities have been studied in long-term care settings. However, the evidence base for effectiveness of these interventions is slim, and the interventions...
themselves are neither well systematized nor widely used in clinical practice. A recent consensus paper on nonpharmacologic strategies for treating apathy in AD addresses the interaction of one-on-one interventions with Information and Communication Technologies. They have also been explored. For cholinesterase inhibitors, several randomized clinical trials have demonstrated modest improvements in apathy. However, about half of the patients showed no significant relief of apathetic symptoms following treatment. Antidepressant medications have not been found to improve apathy in AD and may in fact worsen symptoms. Another pharmacologic treatment that has failed in the treatment of apathy in AD is modafinil, a drug of unclear mechanism. While modafinil may bind weakly to the dopamine and norepinephrine transporters, the histaminergic and orexinergic systems are also thought to be responsible for its pharmacologic effects. Clearly, better pharmacologic options are needed for apathy in AD.

Based on clinical anecdotal reports, methylphenidate is under consideration for the treatment of apathy in AD and has shown encouraging results in initial trials. Understanding the neuronal circuits underlying motivated behavior and their reliance on catecholamine actions helps provide a rationale for methylphenidate actions in the treatment of apathy in patients with mild to moderate AD.

NEUROBIOLOGY AND PHARMACOLOGY OF APATHY

Lesions to Prefrontal Cortical-Basal Ganglia Circuits Induce Apathy

Anatomical, physiological, and behavioral studies have identified parallel, cortical-basal ganglia circuits that govern action, cognition, and emotion and play key roles in motivated behavior (Fig. 1A). Basal ganglia circuits are especially important for mediating habits—often unconscious, complex emotional, cognitive, and motor responses formed from repetitive experience.

Traditional research in rodents has focused on the role of dopamine inputs to the nucleus accumbens in driving motivation. For example, rats normally choose to climb a tall barrier for a small reward, unless they have dopamine depletion from the nucleus accumbens. However, similar motivational deficits occur with insults to the medial prefrontal cortex (PFC). The PFC expands exponentially in primate brains and is essential for the complex and elaborated aspects of motivated behavior in humans. As described below, the degeneration of PFC, as occurs in AD, produces symptoms of apathy. Thus, understanding the distinct contributions of PFC subregions to motivated behavior, for example, as reviewed by Levy or Knight, helps to explain why degeneration of these areas results in apathetic behaviors (Fig. 1B). The relationship of PFC subregions to dimensions of the apathy syndrome is briefly summarized here:

Dorsolateral PFC: The dorsolateral PFC is able to generate top-down goals for future actions by creating internally generated representations that are independent of sensory stimulation. Thus, lesions to the dorsolateral PFC in humans are typified by the loss of a
cognitive plan or goal for actions. This is described sometimes as a “pseudodepressive” syndrome that is characterized by reduced initiative and motivation, flattened affect, reduced verbalizations, and behavioral slowness arising from an inability to plan and maintain sequences of goals and actions.34

**Orbital-ventromedial PFC:** Lesions to these ventral aspects of the PFC cause a loss of emotional evaluation and an inability to link emotional-affective signals to behaviors, consistent with their connections with limbic regions such as the amygdala. A key feature of orbital-ventromedial PFC dysfunction is emotional blunting.37,38 Emotion and affect may reveal the motivational value of a given behavior and orient decision-making.32 In the setting of orbital or ventromedial PFC lesions, a diminished reactivity to emotion and reward may produce a decision-making deficit—that is, an inability to evaluate the emotional consequences of one’s own choices—and a decrease in goal-directed behavior.32,39

**Dorsomedial PFC:** Lesions to the dorsal and medial aspects of PFC often include damage to the anterior cingulate and premotor/supplementary motor areas that are important for the organization and initiation of self-generated behaviors. Thus, these lesions can produce a profound loss of self-initiated action and spontaneous behaviors, which can be temporarily reversed by external stimulation. At its most extreme, lesions to the region of the anterior cingulate can produce akinetic mutism, where patients lose the will to move or talk, even though they are capable of both.34

All of these PFC subregions interconnect,40 and coalesce in “hubs” such as the rostral anterior cingulate.41 They also contribute to cortical-cortical networks involved in additional aspects of motivated behavior. For example, altered PFC connectivity with areas such as the insular cortex has been implicated in symptoms of apathy.42 As the present review is focused on methylphenidate as a treatment for apathy in AD, we will concentrate on PFC subregions where catecholamine and methylphenidate actions have been extensively studied.

**Degeneration of Prefrontal Cortical Circuits in Alzheimer’s Disease and Its Relationship to Symptoms of Apathy**

The PFC circuits needed for motivated, appropriate behavior are disrupted by AD tau and amyloid pathology beginning in Braak Stage III. Cortical tau pathology and subsequent neuronal loss lead to widespread degeneration of the PFC (Fig. 1B), and tau pathology correlates with cognitive impairment.43 In PFC, tau pathology concentrates in layer III and V glutamatergic pyramidal cells, as tangles build inside of neurons and kill them. However, these neurons likely lose function long before they fully degenerate, for example, due to loss of synapses.44 The PFC is also a focus of amyloid pathology.45 In later Braak stages, the entire PFC expresses significant buildup of both tau and amyloid AD degeneration.46

Neuroimaging studies have confirmed that the symptoms of apathy in AD correlate in vivo with pathology in the PFC. These studies have compared AD patients with extensive symptoms of apathy to those at similar stages of disease with minimal apathy. They have found that apathy is correlated with alterations in the PFC, especially in the anterior cingulate, dorsomedial PFC, and orbital PFC regions. Early SPECT imaging studies demonstrated an association between apathy and reduced regional cerebral blood flow in the...
orbitofrontal cortex and anterior cingulate. Similarly, a structural imaging study showed a correlation between apathy and gray matter loss in medial PFC (including anterior cingulate).

The advent of PET radioligands for amyloid and tau has enabled the study of apathy in association with AD-specific neuropathology. PET amyloid imaging with $^{11}$C]PiB has shown a correlation between apathy and the accumulation of fibrillar amyloid in the PFC, including the orbital, ventromedial, and polar PFC subregions, as well as the anterior cingulate. Most recently, tau PET imaging has been used to link apathy with tau pathology in the orbital PFC using $^{11}$C]PBB3 or the right anterior cingulate and dorsolateral PFC using $^{18}$F]flortaucipir. Thus, the neuroimaging findings in AD are consonant with earlier data from lesion studies, and corroborate a major role for PFC insults in apathy.

**Strategy for Treatment: Boosting Actions of Norepinephrine and Dopamine in Prefrontal-Striatal Circuits With Methylphenidate**

Researchers have wondered whether they could lessen symptoms of apathy by administering methylphenidate, a treatment for Attention Deficit Hyperactivity Disorder (ADHD) that is known to improve motivation in non-AD patients. Methylphenidate is thought to have many of its beneficial catecholamine actions in ADHD by strengthening PFC function, and it may boost remaining PFC circuits in AD patients as well. Methylphenidate may also enhance motivation by enhancing dopamine actions in striatum, a region more resilient in AD.

The catecholamines norepinephrine and dopamine are synthesized by neurons in brainstem that project to forebrain, with dense projections to subcortical structures such as the thalamus and striatum, respectively, and a more delicate projection to the cortex, including the PFC. Methylphenidate blocks dopamine transporters and increases extracellular dopamine concentrations in the striatum and in the medial PFC. A comprehensive examination of catecholamine changes (Fig. 2A) made the surprising discovery that methylphenidate produces an even greater increase in norepinephrine than dopamine in rat medial PFC. The low, clinically relevant doses used had greater effects on PFC than those seen subcortically in nucleus accumbens or septum. Thus, methylphenidate effects on PFC catecholamine actions may be particularly important to understanding the clinical benefits of this compound, as described below.

**Catecholamine Actions in Striatum and Thalamus**

The effects of dopamine on striatal physiology and function have been studied extensively. The parallel pathways through the basal ganglia governing motor, cognitive and affective responses all involve the interplay of the Direct and Indirect circuits within the basal ganglia (Fig. 3). The Direct Pathway excites movements, thoughts, and emotions, and is potentiated by DA stimulation of D1R. In contrast, the Indirect Pathway inhibits movements, thoughts and emotions, but is suppressed by DA stimulation of D2R, resulting in the disinhibition of action. Thus, dopamine has an overall excitatory effect in striatum through both D1R and D2R mechanisms. Catecholamine actions in the thalamus have received much less attention than dopamine actions in the striatum. However, recordings
from the thalamus in rats indicate that moderate increases in locus ceruleus activity enhance sensory processing through the thalamus. Of relevance to the current review, systemic administration of methylphenidate enhanced visual processing in lateral geniculate nucleus. Thus, some of methylphenidate’s beneficial actions may occur by enhancing thalamic functions.

**Catecholamines have an Inverted U Dose/Response in PFC**

Both norepinephrine and dopamine have an inverted U dose/response on PFC function, where either insufficient or excessive levels of catecholamines impair PFC function, while moderate levels are essential for optimal function (Fig. 2B). The level of catecholamine release increases with increasing arousal (Fig. 2B), and the amount of catecholamine release can engage different receptors, for example, where moderate levels of norepinephrine during alert waking engage high affinity α2A-AR, while very high levels of norepinephrine release during stress can engage lower affinity receptors, such as α1A-AR. Thus, the level of catecholamine release can serve as a “switch” by engaging differing receptors.

The dorsolateral PFC is able to create goals for action through recurrent, excitatory N-methyl-D-aspartate (NMDA) receptor circuits that can maintain information without sensory stimulation, the foundation of abstract thought and goal-directed behavior. As summarized in Figure 4, the connectivity of these circuits is powerfully controlled by catecholamines, with moderate levels strengthening and refining inputs, and high-level weakening connections. Thus, while low doses of methylphenidate may boost PFC function, these findings caution that excessive catecholamine release in PFC, for example, via doses of methylphenidate that are too high, can worsen PFC function and may be counterproductive to therapeutic strategies. An inverted U dose response on PFC physiology and function has been seen with methylphenidate administration in both rats and monkeys.

**Methylphenidate Effects in Human Subjects**

In contrast to animal studies where within-subjects dose-response studies are common, understanding the methylphenidate dose-response on PFC executive function requires between study comparisons, and can reflect differing results between individuals with ADHD and those with healthier PFC abilities. For example, a meta-analysis of therapeutic doses of methylphenidate in ADHD patients shows improved executive functioning and enhancement of PFC activity measured with fMRI. However, studies of cognition in humans rarely administer high doses, and thus a true dose/response curve cannot easily be assessed. A meta-review of single-dose studies of methylphenidate in adults indicates that it is the lower doses (e.g., 10-20 mg) that are more optimal for working memory and paired associates learning, while higher doses (e.g., 40-60 mg) can actually impair performance and that the optimal dose for impulse control may differ from that for working memory.

Positron emission tomography (PET) imaging has enabled investigators to relate doses of methylphenidate to catecholamine transporter occupancy. The estimated dose of oral methylphenidate required to block 50% of dopamine transporters in striatum (ED50) corresponded to 0.25 mg/kg, and of norepinephrine transporters in thalamus and other
norepinephrine transporter-rich areas to 0.14 mg/kg. Therefore, the average efficacious maintenance doses of methylphenidate in ADHD (0.35-0.55 mg/kg) occupy 70%-80% of norepinephrine transporters but only 60%-70% of dopamine transporters. Those findings are consistent with the higher in vitro affinity of methylphenidate for norepinephrine transporters than dopamine transporters and suggest the potential relevance of norepinephrine transporter inhibition in the therapeutic effects of methylphenidate.

PET studies have also permitted the effect of methylphenidate on extracellular levels of dopamine to be translated from animals to human brain. Volkow et al. showed that oral methylphenidate (average dose 0.8 mg/kg) significantly increased extracellular dopamine in the brains of healthy control subjects, as evidenced by a significant 20% reduction in D2 receptor availability in striatum. A subsequent study by Clatworthy et al. reported that methylphenidate effects on dopamine release ([11C]-raclopride receptor availability) in differing striatal subregions of young healthy subjects correlated with performance on a working memory versus reversal task. These results provide direct evidence that oral methylphenidate at doses within the therapeutic range significantly increases extracellular dopamine in human brain. Unfortunately, data on increases in extracellular norepinephrine in human brain by therapeutic doses of methylphenidate are not available, and PET imaging to detect a catecholamine receptor signal is limited to subcortical brain regions.

**Caveats and Limitations**

Several cautionary notes must be kept in mind when exploring methylphenidate as a therapeutic for apathy in AD. First, the dose of methylphenidate must be optimized, as elderly patients may have changes in bioavailability and drug metabolism. As described above, high doses can worsen PFC function, as well as having worrisome side effects such as tachycardia. Previous and current studies of apathy in AD have not attempted a thorough exploration of the safety and efficacy of methylphenidate at doses greater than 20 mg/day. However, these doses are based on longstanding clinical experience in older adults, and not all participants with apathy in AD are able to tolerate a dose of 20 mg/day. Therefore, higher doses may not be feasible in this population. Second, the degenerative course of the disease will likely limit the beneficial actions of methylphenidate, due to neurofibrillary tangle accumulation in locus ceruleus neurons, reduced catecholamine concentrations in the aging cortex as compensatory mechanisms become inadequate, and the eventual degeneration of the PFC pyramidal cell circuits that guide motivated behavior. Under these decorticate conditions, increasing dopamine actions in the basal ganglia may remain, but may produce agitation and perseveration rather than enhanced motivation. Third, this review considers methylphenidate for apathy as a syndrome in isolation, whereas it frequently co-occurs with other neuropsychiatric symptoms, particularly depression. Since we excluded current diagnosis of major depressive episode in our previous and current trials, they will not address, for example, how methylphenidate may interact with traditional antidepressants or may enhance motivation to participate in nonpharmacologic interventions for depression in AD. Future studies will need to address these and other issues for patients with AD and multiple neuropsychiatric symptoms.
CONCLUSION

In this review, we have attempted to establish the public health and clinical significance of the apathy syndrome in AD, as well as the unmet need for better treatment of the symptoms of apathy. The catecholaminergic treatment methylphenidate is currently under consideration for the treatment of apathy in AD. Understanding the neuronal circuits subserving motivated behavior and their reliance on catecholamine actions provides a rationale for methylphenidate in the treatment of apathy in patients with AD. Anatomical, physiological, and behavioral studies have identified parallel, cortical-basal ganglia-thalamic circuits that govern action, cognition, and emotion and play key roles in motivated behavior. Understanding the distinct contributions to motivated behavior of subregions of the PFC—dorsolateral, orbital-ventromedial, dorsomedial—helps to explain why degeneration of these areas results in apathetic behaviors. We propose that the degeneration of the PFC in AD produces symptoms of apathy. We further propose that methylphenidate treatment may ameliorate those symptoms by boosting norepinephrine and dopamine actions in prefrontal-striatal-thalamocortical circuits.

Initial trials of methylphenidate for the treatment of apathy in AD have yielded encouraging results. In a Phase II trial (ADMET), methylphenidate (up to 10 mg orally twice daily) showed significant improvement in symptoms of apathy compared to placebo. More recently, Padala et al. reported that in male veterans with mild AD and apathy, this same dose of methylphenidate treatment significantly improved apathy, as well as cognition, functional status, caregiver burden, depression, and clinical global impression of change after 12 weeks of treatment. Both of these preliminary studies found methylphenidate at these doses to be safe and well tolerated in this population. The primary aim of the ADMET 2 study is to determine whether methylphenidate is effective in improving clinically significant apathy in a larger sample of 200 participants with AD, over a longer 6-month treatment period.

Directions for Future Research

ADMET 2 will still leave unanswered several important questions about the neurobiology of apathy and the neurobiology of methylphenidate treatment. A blood-based biomarkers administrative supplement for the ADMET 2 grant provides for collection of blood specimens in a portion of the participants to generate preliminary data about a number of potential biomarkers of apathy and its treatment in AD. The objectives are to understand biomarker correlates of apathy and of change in apathy over time, and to identify possible predictors of treatment response. In the original ADMET trial, a distinct group of approximately one-third of the sample had a dramatic response to treatment, but another third showed minimal improvement, and the final third had no benefit from treatment. Importantly, no significant clinical differences were observed between responders and nonresponders, suggesting that biomarker information may be necessary for prediction of treatment response. In order to elucidate this heterogeneity of response, the biomarker substudy of ADMET 2 will investigate a number of specific blood-based biomarkers, including microRNA (focused on dopamine and norepinephrine transporters), lipidomics, and markers of oxidative stress, inflammation (cytokines), and neuronal loss (S 100

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calcium binding protein B, neurofilament light chain protein). This substudy will generate preliminary data about promising blood-based biomarkers that may be further evaluated in a larger sample.

Apart from blood-based biomarkers, PET studies may yet elucidate the relative contribution of dopaminergic versus noradrenergic contributions to apathy and to methylphenidate treatment response. Longitudinal PET studies could be undertaken to compare brain dopamine and norepinephrine transporter binding in the same AD participants—to determine their relative associations with baseline apathy and longitudinal change in apathy, and to determine the predictive value of these PET measures for methylphenidate treatment response.

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FIGURE 1.
Prefrontal cortical brain regions that mediate motivated behavior affected in Alzheimer’s disease. (A) Prefrontal cortical-basal ganglia circuits that play key roles in motivated behavior. Dashed lines represent indirect connections. (B) Tau pathology afflicts prefrontal cortical circuits, mediating motivated behaviors beginning in Braak Stage III/IV. dmPFC: dorsomedial prefrontal cortex; dPFC: dorsolateral prefrontal cortex; oPFC: orbital prefrontal cortex; ACC: anterior cingulate cortex. Premotor: premotor cortex.
FIGURE 2.
Actions of methylphenidate via catecholamines in prefrontal cortex. (A) Methylphenidate has greater effects on catecholamine levels in prefrontal cortex than in subcortical structures in rat brain. (B) Catecholamines have an inverted U dose response on prefrontal top-down control, where either too little or too much is detrimental to function. The beneficial effects of moderate norepinephrine levels are through high affinity, postsynaptic alpha-2A-AR, while the detrimental actions at high levels of norepinephrine release are through low affinity alpha-1-AR. In contrast, dopamine has both beneficial and detrimental actions through increasing engagement of D1R. PFC: prefrontal cortex, MSA: medial septal area, NAc: nucleus accumbens. Adapted from Berridge and Arnsten, 2013.53
FIGURE 3.
Dopamine effects on basal ganglia circuitry. The basal ganglia have parallel circuits for the control of movement, cognition, and emotion. The basal ganglia regulate the output of the thalamus, and its ability to excite the cortex. There are two major pathways emanating from the striatum: a Direct pathway that overall excites thalamocortical projections (by inhibiting the inhibitory effects of Gpi/SNr on thalamus), and an Indirect pathway that overall inhibits thalamocortical projections (by a still more complex series of connections). Dopamine facilitates movements, thoughts, and emotions by exciting the Direct pathway via D1R, and inhibiting the Indirect pathway via D2R. DA: dopamine; Thal-Cort: thalamo-cortical; GPe: globus pallidus external segment, GPi: globus pallidus internal segment; SubTh: subthalamic nucleus; SNc: substantia nigra pars compacta; SNr: substantia nigra pars reticulate; VTA: ventral tegmental area.
FIGURE 4.
Catecholamine effects on prefrontal cortical connectivity. Catecholamines have powerful effects on the connectivity of prefrontal cortical recurrent excitatory circuits needed to generate top-down goals for action. These newly evolved synapses rely on N-methyl-D-aspartate (NMDA) receptors for neurotransmission. They also contain the molecular machinery to rapidly weaken connections through feedforward calcium-cAMP signaling, opening nearby potassium (K⁺) channels to functionally disconnect the circuit. Moderate levels of catecholamine release strengthen connectivity, through alpha-2A-AR inhibiting cAMP opening of K⁺ channels. D1R within the synapse may also enhance firing by phosphorylating NMDA receptors to maintain them within the synapse. In contrast, excessive catecholamine release weakens connectivity by driving calcium-cAMP opening of K⁺ channels through alpha-1AR and D1R actions at locations away from the synapse. For more detailed discussion of this topic, see the following video on how stress and fatigue can alter prefrontal function: https://www.youtube.com/watch?v=vdDvChLuQsA&t=6s.