










**REVIEW ARTICLE**

# Agitation and impulsivity in mid and late life as possible risk markers for incident dementia

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**Abstract**

To identify knowledge gaps regarding new-onset agitation and impulsivity prior to onset of cognitive impairment or dementia the International Society to Advance Alzheimer's Research and Treatment Neuropsychiatric Syndromes (NPS) Professional Interest Area conducted a scoping review. Extending a series of reviews exploring the pre-dementia risk syndrome Mild Behavioral Impairment (MBI), we focused on late-onset agitation and impulsivity (the MBI impulse dyscontrol domain) and risk of incident cognitive decline and dementia. This scoping review of agitation and impulsivity pre-dementia syndromes summarizes the current biomedical literature in terms of epidemiology, diagnosis and measurement, neurobiology, neuroimaging, biomarkers, course and prognosis, treatment, and ongoing clinical trials. Validations for pre-dementia scales such as the MBI Checklist, and incorporation into longitudinal and intervention trials, are needed to better understand impulse dyscontrol as a risk factor for mild cognitive impairment and dementia.

**KEYWORDS**

agitation, disinhibition, impulse dyscontrol, impulsivity, MBI, mild behavioral impairment, pre-dementia

## 1 | INTRODUCTION

Neuropsychiatric symptoms (NPS) are non-cognitive behavioral or psychiatric symptoms in dementia or pre-dementia syndromes and are also sometimes referred to as behavioral and psychological symptoms of dementia (BPSD). Clinicians have been aware of NPS as a manifestation of dementia since the time of Alois Alzheimer and his description of the first patient with Alzheimer's disease (AD), who besides showing rapid cognitive decline, displayed NPS in the form of paranoia, agitation, and hallucinations.<sup>1</sup> The Cardiovascular Health Study found that 75% of dementia patients experienced a neuropsychiatric symptom in the month prior to evaluation,<sup>2</sup> while the Cache County Study found the 5-year period prevalence of NPS to be 97% in patients with dementia.<sup>3</sup> NPS are associated with worse disease prognosis<sup>4</sup> and earlier death.<sup>5</sup> NPS also presents in mild cognitive impairment (MCI), although less frequently than in dementia, with NPS in MCI prevalence estimates ranging from 31% to 60%.<sup>6,7</sup> These NPS in MCI are more prevalent in the clinical versus community settings, underscoring their clinical significance.<sup>8</sup>

For decades, cognitive symptoms were given priority in the diagnosis of dementia, although in many cases NPS preceded or accompanied cognitive symptoms. More recently, an AD variant has been described in which a dysexecutive or behavioral syndrome manifests prior to cognitive symptoms.<sup>9</sup> Similarly, behavioral symptoms frequently present as the first clinical signs of frontotemporal dementia (FTD).<sup>10</sup> Often, patients with this type of neuropsychiatric presentation will seek out psychiatric consultation and receive a diagnosis of a primary psychiatric disorder, without consideration of a potential prodromal or pre-

dementia syndrome.<sup>11</sup> There is evidence and increasing consensus that NPS can be an early manifestation of dementia in cognitively asymptomatic subjects or in those with MCI.<sup>12,13</sup> Studies in the general population<sup>6,14</sup> and in clinical cohorts support the idea that NPS in MCI increase the risk of incipient dementia, with an annual progression rate of 25% in MCI with NPS<sup>15,16</sup> versus an annual general conversion of 10%-15%.<sup>17</sup> Likewise, the presence of NPS in cognitively normal older adults also increases the progression to dementia, as indicated by several studies, such as the Alzheimer's Disease Cooperative Study,<sup>18</sup> the Psychiatric Registry and Danish Physician,<sup>19</sup> the Mayo Clinic Study of Aging,<sup>20</sup> the Medical Research Council Cognitive Function and Aging Study,<sup>21</sup> and the National Alzheimer's Coordinating Center (NACC).<sup>22-24</sup> Recently, an analysis of 1988 NACC participants demonstrated that NPS precede cognitive symptoms 59% of the time across dementias, and even in AD, 30% of participants developed neuropsychiatric symptoms in advance of cognitive symptoms.<sup>25</sup> These data emphasize the importance of later-life onset of NPS in dementia risk assessment.

The Alzheimer's Association International Society to Advance Alzheimer's Research (ISTAART) NPS professional interest area (PIA), identified in 2012 the need to set an agreed upon construct and definition for NPS pre-dementia syndromes. Building on the prior definitions of a pre-dementia risk state by Taragano et al.<sup>12,13</sup> and frontotemporal-MCI by de Mendonca et al.,<sup>10</sup> the ISTAART NPS-PIA formally described mild behavioral impairment (MBI) as the emergence of sustained and impactful NPS occurring after the age of 50, which are not captured by traditional psychiatric nosology, persist for at least 6 months, and manifest in advance of or in concert with MCI.<sup>26,27</sup> Operationalized,

the ISTAART MBI research definition required change in at least one of five areas of personality and behavior: (a) decreased motivation (eg, apathy, spontaneity, indifference); (b) affective dysregulation (eg, anxiety, dysphoria, changeability, euphoria, irritability); (c) impulse dyscontrol (eg, agitation, disinhibition, gambling, obsessiveness, behavioral perseveration, stimulus bind); (d) social inappropriateness (eg, lack of empathy, loss of insight, loss of social graces or tact, rigidity, exaggeration of previous personality traits); and (e) abnormal perception or thought content (eg, delusions, hallucinations).<sup>26</sup> Thus, MBI represents the neurobehavioral axis of pre-dementia risk states, and complements the traditional neurocognitive axis represented by subjective cognitive decline (SCD) and MCI.

This scoping review follows the definition proposed by Colquhoun et al. in 2014, where a, "Scoping review is a form of knowledge synthesis that addresses an exploratory research question aimed at mapping key concepts, types of evidence, and gaps in research related to a defined area or field by systematically searching, selecting and synthesizing existing knowledge."<sup>28</sup> Scoping reviews describing the evidence for neuropsychiatric symptom sets as predictors of dementia have been completed for the other MBI domains of decreased drive/motivation,<sup>29</sup> affective/emotional dysregulation,<sup>30</sup> social inappropriateness,<sup>31</sup> and abnormal perception and thought content.<sup>32</sup> The purpose of this scoping review is to describe the current evidence and identify gaps in the biomedical literature for the epidemiology, neurobiology, neuroimaging, biomarkers for blood and cerebrospinal fluid (CSF), prognosis, and completed and ongoing trials for treatment of later-life impulsivity and agitation as predictors of dementia. As such, there are different sections specific to each of the previously named categories. It is important to understand the prevalence of agitation and impulsivity in pre-dementia syndromes as there is a potential opportunity for early intervention and higher impact in this early stage of illness. The number of studies in the completed search that met full inclusion criteria were too numerous (n = 136) to include every study in this review paper. Thus, the authors summarized the most pertinent and included as many studies as was reasonably possible.

## 2 | METHODOLOGY

A comprehensive search of the biomedical literature was performed by a medical librarian using the following databases: Ovid MEDLINE, PubMed (for non-MEDLINE records), Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and PsycInfo.

Searches for Ovid MEDLINE, PubMed, Embase, CINAHL, and PsycInfo were initially performed in January and February 2018, and then updated on April 26, 2019. The search strategies for each database are reported in Supplement 1.

Abstracts and full-text articles were screened by a team of reviewers—S.G., S.H., Z.I., M.M., and D.B. A third reviewer acted as a tie breaker when the initial two reviewers were unable to come to agreement. Abstract screening was conducted in Covidence, an online software that allows reviewers to access and resolve inclusion/exclusion conflicts, as well as track the progress of other reviewers, thus improv-

### RESEARCH IN CONTEXT

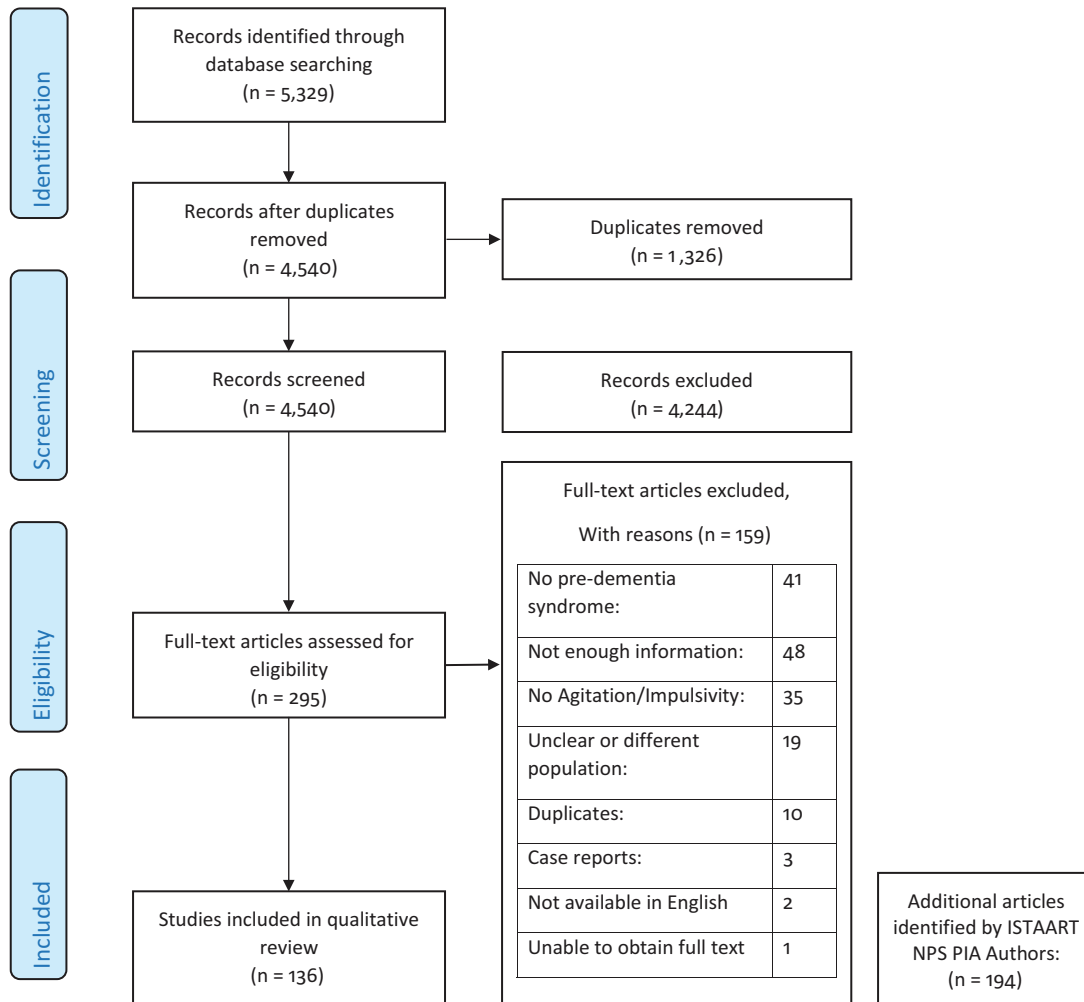
1. Scoping Review: MEDLINE, PubMed, Embase, CINAHL, and PsycInfo were searched for impulse dyscontrol and agitation keywords in pre-dementia and dementia populations. A total of 4540 abstracts were screened in duplicate, 295 selected for full-text review and 136 included in the final manuscript.
2. Interpretation: The research in agitation is more robust than that for impulsivity, in part due to a poorly established definition of impulsivity. Nonetheless, early evidence suggests that later life onset of Impulse Dyscontrol, a domain in the pre-dementia risk syndrome Mild Behavioral Impairment, is important to explore in determining risk of dementia.
3. Future Directions: We describe the ongoing and future research agenda for study of Impulse Dyscontrol for dementia prognostication and early detection. This agenda includes improving measurement, including fluid and imaging biomarkers in cross-sectional and longitudinal trials, and assessing the role of different interventions in mitigating symptoms and decreasing risk of incident cognitive decline and dementia.

ing the efficiency of conducting a review. Duplicates were removed using EndNote.

Inclusion criteria were studies focused on pre-dementia or MCI, and NPS or BPSD. Other dementias such as behavioral variant frontotemporal dementia (bvFTD), vascular dementia (VasD), dementia with Lewy bodies (DLB) and Parkinson disease dementia were included if there was a focus on NPS in individuals with pre-dementia. Studies with an elderly population with cognitive impairment and NPS were also included.

Exclusion criteria were other disease focus such as subjects with Down syndrome, Huntington disease, dementia due to human immunodeficiency virus, or traumatic brain injury (TBI). Studies without pre-dementia, MCI, NPS, or BPSD were excluded. In addition, animal and non-English studies were excluded.

A total of 5329 citations/abstracts were retrieved through searches of these databases. From this total, 1326 duplicates were removed, resulting in a final set of 4540 citations/abstracts for review. Following screening, 295 articles were selected for full-text review. From that subset, 136 full-text articles were included in the review. Studies that included a minimum of three subjects and met inclusion criteria were then reviewed by the authors for clinical relevance and research quality. Publications that included overlapping patient samples were culled and the most salient publication was included. In addition, 194 articles were identified independently by authors and included in the scoping review (See Figure 1).<sup>33</sup>



**FIGURE 1** PRISMA Flow Diagram

### 3 | EPIDEMIOLOGY

NPS are common in patients with MCI, occurring in 35%-75% of individuals.<sup>34</sup> The International Psychogeriatric Association (IPA) 2015 Consensus Provisional Definition of Agitation in Cognitive Disorders defines agitation broadly as: "(1) occurring in patients with a cognitive impairment or dementia syndrome; (2) exhibiting behavior consistent with emotional distress; (3) manifesting excessive motor activity, verbal aggression, or physical aggression; and (4) evidencing behaviors that cause excess disability and are not solely attributable to another disorder (psychiatric, medical, or substance-related)."<sup>35</sup> Agitation is one of the most common NPS reported in MCI patients; however, prevalence estimates vary drastically from 5% to 25% in population-based studies,<sup>34</sup> and 4% to 45% in hospital-based studies.<sup>36</sup> These wide ranges are likely due to differences in patient setting (population-based vs clinical trial setting), MCI diagnostic criteria used (amnesic vs non-amnesic), differences in scales used to assess agitation, and the exclusion of patients with depressive symptoms in some studies (InDDEX trial).<sup>37</sup>

Of interest, in a longitudinal population-based study by Copeland et al., agitation was more prevalent in patients who had a CDR score

of 0.5, and progressed to AD (36% at baseline) than in patients who remained stable at a CDR score of 0.5 (18% at baseline), compared to patients who had a CDR score of 0 at baseline and follow-up (6%).<sup>38</sup>

In the Mayo Clinic Study of Aging, in 2008, Geda et al. reported that in 1969 non-dementia patients,<sup>39</sup> the prevalence of agitation and irritability was greater in patients with amnesic compared to non-amnesic MCI, and that Neuropsychiatric Inventory (NPI)-measured disinhibition, which some have categorized as an impulsive behavior, was more prevalent in patients with non-amnesic compared to amnesic MCI. These findings are corroborated by a large cross-sectional cohort study with 512 patients diagnosed with MCI, which found that aggressive symptoms were more prevalent in patients with single-domain amnesic MCI, compared to patients with single-domain non-amnesic and multi-domain MCI. Disinhibition was also found to be more prevalent in patients with single-domain non-amnesic MCI as compared to single-domain amnesic and multi-domain MCI.<sup>40</sup> On the contrary, in 2011, Rosenberg et al. found that the prevalence of NPS such as agitation and disinhibition did not differ between patients with amnesic compared to non-amnesic MCI. However, the authors also reported that in patients with MCI and executive dysfunction, NPS

were more frequent including agitation, irritability, and disinhibition, along with depression, anxiety, apathy appetite, and sleep disturbances than in MCI patients without executive dysfunction.<sup>41</sup>

Compared to agitation, impulsivity has not been well studied in patients with dementia, likely due to imprecise characterization of impulsivity, and few scales available to assess this NPS in this population group. As such, the data available on the prevalence of impulsivity in pre-dementia states are very limited. However, a number of recent studies have worked to characterize the prevalence of impulse dyscontrol in pre-dementia populations. Creese et al., received completed MBI Checklist<sup>27</sup> from 10,952 individuals over the age of 50 with no diagnosis of dementia, and found an overall prevalence of behavioral disturbances in 47.5% of respondents and prevalence of impulse dyscontrol in 31% of respondents.<sup>42</sup>

Data published on the PArkinson's disease Cognitive impairment Study, a large, cross-sectional, hospital-based study of two movement disorder centers in southern Italy, found a cumulative prevalence of MBI of 84.1% in 429 non-demented subjects with Parkinson disease (PD).<sup>43</sup> Prevalence of impulse dyscontrol in the same cohort differed according to disease progression, with 35.5% among those with  $\leq 1$  year of PD versus 47.6% of those with PD  $> 1$  year ( $P = .021$ ).<sup>43</sup> Another study of 326 subjects with PD found the prevalence of impulse control disorders (ICDs) in PD patients with normal cognition, MCI, and dementia to be 55%, 50%, and 42% respectively.<sup>44</sup>

In a large retrospective study of 3,456 patients with MCI from the NACC data set, Apostolova et al. (2014) used factor analysis to group NPI items into four different factor groups: affective behaviors (depression, apathy and anxiety); distress/tension behaviors (irritability and agitation); impulse control behaviors (disinhibition, elation and aberrant motor behavior); and psychotic behaviors (delusions and hallucinations).<sup>45</sup> Impulse control behaviors included disinhibition, elation, and aberrant motor behaviors. The author reported that male gender was significantly associated with all NPS factors (including distress/tension and impulse control). In addition, younger age was associated with an increased prevalence of distress/tension, impulse control, and psychotic behaviors, and lower education was significantly associated with the presence of distress/tension behaviors only.<sup>45</sup>

Posttraumatic stress disorder (PTSD) has been identified as a risk factor for development of dementia in both female<sup>46</sup> and male combat veteran populations.<sup>47-49</sup> At this time, studies assessing whether the combined presence of agitation and PTSD or impulsivity and PTSD predict dementia have not been completed. The two studies that examined whether veterans with PTSD and dementia had higher rates of agitation as compared with patients with dementia without PTSD showed no significant differences in agitation rates between the two different populations.<sup>50,51</sup>

Late life depression has also been well described as a risk factor for development of dementia,<sup>52</sup> but recent evidence has also explored depression as a prodrome.<sup>53</sup> Several large longitudinal cohort studies have suggested that assessment of depression in the context of the overall natural history of symptoms is essential to distinguishing between depression as risk factor or prodrome. These studies demonstrate that the later in life the onset of psychiatric symptomatology,

the more likely these symptoms represent the early stages of a neurodegenerative process that precede dementia by 5-11 years.<sup>30</sup> This distinction, incorporating age of onset and past history of symptoms, is at the crux of appreciating the relationship between neuropsychiatric symptomatology and risk of dementia and is consistent with the overall concept of MBI. This logic applies to new-onset impulsivity and agitation as well.

Impulsive behaviors are considered to be a hallmark of bvFTD.<sup>54</sup> However, findings from a retrospective case study of bvFTD patients suggest that impulsive behaviors may be detected in the pre-dementia stages as well.<sup>10</sup> The authors also proposed frontotemporal-MCI criteria, which are available for further validation on larger samples and longitudinal follow-up.<sup>10</sup>

In a 1-year longitudinal observational study with 76 elderly individuals 60 years of age and older, Tamam et al. investigated the prevalence of ICDs using the self-administered Minnesota Impulse Disorders Interview (MIDI), and impulsivity using the Baratt Impulsiveness Scale Version 11 (BIS-11). The authors reported that  $\approx 22\%$  of the participants had at least one ICD.<sup>55</sup> The most common ICD was intermittent explosive disorder (15.8%), followed by pathological gambling (9.2%). Although these participants were followed for only 1 year, the results of this study suggests that approximately one in five patients over the age of 60 have at least one ICD, and additional longitudinal research is required to assess ICDs as a potential risk factor for cognitive decline and dementia.<sup>55</sup> Older adults with normal cognition can also experience impulse control or disinhibition, albeit less frequently as compared to those with MCI or dementia. Impulsivity, as assessed by the NPI Disinhibition item, seems to be infrequent in non-demented elderly individuals in community and clinical settings.<sup>20,34,36,56,57</sup>

The highlighted literature demonstrates that the prevalence estimates of agitation and impulsivity vary drastically between studies. In total, these findings support that agitation is a prevalent NPS in patients at risk for developing dementia, and that impulsive behaviors may also present as an individual NPS, or co-occur with agitation. It should be noted that almost all of the described studies are cross-sectional in nature and do not get at the important issues of agitation and impulsivity as a risk factor for cognitive or functional decline and incident MCI.

## 4 | DIAGNOSIS AND MEASUREMENT

A valid detection and diagnosis of NPS depends heavily on the choice of a good measure. A variety of scales exist, with differences in symptoms of interest (overall behavioral changes vs specific constructs), assessor (patient, caregiver, or clinician), time frame (eg, 1 week vs 6 months), and symptom dimensions assessed (frequency, severity, or distress). The scales described below—the Cohen-Mansfield Agitation Inventory (CMAI),<sup>58</sup> The Brief Agitation Rating Scale (BARS),<sup>59</sup> the Overt Agitation Severity Scale (OASS),<sup>60</sup> the Agitated Behavior in Dementia Scale (ABID),<sup>61</sup> and the Pittsburgh Agitation Scale (PAS)<sup>62</sup> and variations of the NPI<sup>63,64</sup>—were designed and validated for dementia populations. The number of agitated behaviors or characteristics



of agitation described vary depending on the scale: CMAI, 29; BARS, 10; OASS, 47; ABID, 16; PAS, 4; and the NPI, 8 (NPI-Q, 1 and NPI-C, 21; agitation & aggression). Many items included in these scales describe behavior relevant to patients with mild to severe dementia and may not apply to community-dwelling older adults without dementia. None of these scales were designed for pre-dementia populations. However, the CMAI, NPI, NPI-Q, and NPI-C were studied in MCI populations.<sup>65–68</sup>

The CMAI was developed to systematically assess agitation in people with dementia, often in nursing homes. It consists of 29 descriptions of agitated behaviors, each rated on a 7-point scale based on frequency, ranging from never manifesting the behavior (score of 1) to manifesting the behavior several times an hour (score of 7), with a possible score range of 29–203.<sup>58</sup> Four different agitation factor sub-scores on the CMAI have been identified and are used as secondary outcome measures: (1) aggressive physical behavior (hitting, kicking, pushing, scratching, tearing things, and cursing); (2) nonaggressive physical behavior (pacing, inappropriate robing or disrobing, repetitious sentences or questions, trying to get to a different place, general restlessness, handling things inappropriately and repetitious mannerisms); (3) verbally aggressive behavior (complaining, constant request for attention), and (4) verbally nonaggressive behavior (negativism, repetitious sentences or questions and complaining).

Despite the dementia-centric language, the CMAI was administered to an MCI population in a recent Belgian study, which suggested a different pattern of agitated behaviors. Compared to agitated AD patients, agitated MCI patients presented with significantly less (verbally and physically) aggressive behavior (1% vs 19%) and physically non-aggressive behavior (41% vs 80%), but more verbally agitated behavior (83% vs 76%).<sup>69</sup> However, the CMAI was designed and validated in those with more severe disease. A slightly different symptom manifestation early in the course of the disease may be one of the reasons for contrasting findings in NPS prevalence when general scales are used, suggesting that early symptom manifestations may require more sensitive screening questions, or those designed specifically for pre-dementia populations.

Of general psychopathology scales, the NPI is the most commonly used both in research and clinical practice.<sup>63</sup> The NPI begins with a screening question for each of the 12 neuropsychiatric domains, answered by a close informant in an interview. In case of a positive answer, a subset of questions specifies the depth and complexity of the domain. The scale provides information on frequency, severity, and caregiver distress of the specific domain within the past month. However, in 2005, it was found that only 28.6% of large European memory clinics used the NPI routinely to assess patients with cognitive impairment.<sup>70</sup>

A short version of the NPI, the Neuropsychiatric Inventory–Questionnaire (NPI-Q), includes screening questions, symptom severity, and caregiver distress in the instrument. It was designed to facilitate the screening of NPS in clinical practice.<sup>71</sup> Due to its time-efficiency the NPI-Q has been incorporated into research and into cognitive batteries, such as the Uniform Data Set (UDS).<sup>72</sup> However, for the agitation/aggression domain, a screening question “Does the patient

have periods when he/she refuses to cooperate or won't let people help him/her? Is he/she hard to handle?” may not cover the variety of agitated behaviors present in the pre-dementia population, thus leading to under-reporting. An NPI-Q agitation/aggression subscale, originally developed in nursing home residents may address this issue.<sup>73</sup> It consists of four NPI-Q items that emerged as a symptom cluster in several factor analyses including agitation/aggression, irritability, aberrant motor behavior, and disinhibition. Although requiring further validation, according to a comparative study of NACC and ADNI cohorts, the scale appears to be a promising index of agitation in patients with MCI.<sup>66</sup>

Another potentially useful subscale for future studies may be the Agitation subscale from the Neuropsychiatric Inventory–Clinician (NPI-C), a clinician rated version of the NPI.<sup>64</sup> The Agitation/Aggression item from the original NPI has been separated into NPI-C Agitation and NPI-C Aggression, with an option of both domains to be used as standalone measures.<sup>64</sup> The authors report a significantly stronger correlation of NPI-C Agitation domain with the CMAI compared to the original NPI Agitation/Aggression, suggesting that the revised domain is a more comprehensive measure of agitation. The domain separation also appears to be clinically relevant, as in one study using semi-structured interviews, agitation was found to be more prevalent than aggression in MCI.<sup>67</sup> In addition, significant differences were reported in agitation prevalence between patients with MCI and mild AD, but this did not apply to aggression.<sup>67</sup> Incorporating the clinician's judgment is also considered valuable when investigating the pre-dementia population, mainly because of differences found between agitation severities rated by clinicians versus caregivers.<sup>68</sup> Future studies are needed to confirm the diagnostic utility of NPI-C in pre-dementia stages. One disadvantage of the NPI-C compared to NPI or NPI-Q is the longer administration time, particularly because the instrument is designed so that all questions are asked and there is no screening question or any “skip-out” of subsequent questions for any NPI-C domain, as there is in the NPI.

The Barratt Impulsiveness Scale (BIS-11) and Behavioral Inhibition and Behavioral Activation Scales (BIS/BAS) are self-report questionnaires that have been commonly used in psychiatry. The BIS-11 is a 30-item scale assessing three dimensions: attentional, motor, and non-planning impulsiveness.<sup>74,75</sup> The BIS/BAS is a self-report measure including four dimensions: behavioral inhibition, reward responsiveness, drive, and fun seeking.<sup>76</sup> A recent functional magnetic resonance imaging (fMRI) study on individuals with SCD using these scales reported that although SCD participants made fewer future-oriented decisions compared to healthy controls on a behavioral task, no significant differences were found between the groups on both scales except a slight, but significantly lower score on the BIS/BAS drive dimension.<sup>77</sup> In contrast, a large Australian study of non-demented, community-dwelling 60- to 64-year-old adults found significant differences on the BIS/BAS behavioral inhibition subscale between those with memory complaints and those without.<sup>78</sup>

Despite these findings, various issues need to be acknowledged when considering using the previously described questionnaires in the pre-dementia population. The questionnaires measure long-term

patterns without relation to a time frame. Therefore, they may not be sensitive to possible late-life behavioral change. In addition, self-report questionnaires may produce slightly different results compared to informant-rated measures. Regarding the latter, the BIS scale has been recently modified into an informant-rated scale and has become part of the NACC database UDS-FTLD module.<sup>79</sup> Although more research is needed in this area, it does seem that new or revised scales may be required for detecting subtle changes in impulsive behavior.

Recently, a new time-efficient, informant-based questionnaire, the Mild Behavioral Impairment—Checklist (MBI-C), has been introduced, with items designed specifically to detect subtle changes in persons with no more than MCI.<sup>27</sup> The MBI-C stipulates later-life emergence of symptoms and a 6-month period of symptom persistence as opposed to 1- to 4-week time frame of the other NPS scales, which helps to exclude various transient reactive states (eg, medication, sleep deprivation, etc), decreasing false positives. Of the five MBI domains, the impulse dyscontrol domain provides assessment of agitation, aggression, and impulsivity symptoms. The MBI-C is the first measure developed specifically for the pre-dementia population, and the ongoing validation studies<sup>42,80–85</sup> will determine its diagnostic utility. Early validation results have determined cut-points for MBI diagnosis in SCD<sup>85,86</sup> and MCI, and have demonstrated a five-factor model for the MBI-C with an intact impulse control/agitation domain,<sup>42,87</sup> test-retest reliability, construct validity, and discriminative validity from the NPI.<sup>84,85</sup> Furthermore, a 1-year longitudinal study has shown the emergence of MBI with cognitive decline in cognitively normal older adults.<sup>42</sup>

Overall, the evidence suggests that there are many scales used to assess NPS without validation in the pre-dementia population, a trend that has been observed previously across European centers.<sup>70</sup> As such, future investigations are encouraged to use validated scales of NPS specific to the pre-dementia population. However, different definitions of agitation have impeded systematic study of this syndrome. In response to this clinical and research gap, the IPA developed criteria for agitation in dementia in which symptoms are divided into the domains of excessive motor activity, verbal aggression, and physical aggression domains.<sup>35</sup> Of note, the criteria extend back to the MCI phase, but not to older adults with normal cognition, and have yet to be operationalized into a validated rating scale.

## 5 | NEUROBIOLOGY OF AGITATION AND IMPULSIVITY

Clinicopathological studies suggest that the dorsolateral prefrontal, orbitofrontal, and anterior cingulate cortices are important for emotional regulation and processing, through their interactions with the sensory cortex, amygdala, and the medial temporal regions.<sup>88,89</sup> Damage to one or more of these regions results in emotional dysregulation, including disinhibition, aggression, and agitation.<sup>88</sup> In individuals with AD, the severity of agitation correlates with the extent of neurofibrillary tangle pathology in the bilateral orbitofrontal cortices and anterior cingulate regions,<sup>89</sup> and with the degree of temporal limbic cortical hypoperfusion on 18F-fluorodeoxy-glucose positron emission tomog-

raphy (PET).<sup>90</sup> Consistent with these findings, studies using the tau tracer 18F-THK5351 in cognitively impaired individuals have shown associations between irritability and tau burden in the bilateral mesial frontal, bilateral dorsolateral prefrontal, right temporal pole, and right superior temporal cortices.<sup>91</sup> In preclinical AD, higher NPI scores, particularly measures of irritability/lability and sleep/nighttime behavior, predicted subsequent hypometabolism in the posterior cingulate cortex over 2 years,<sup>92,93</sup> which supports the notion that such behavioral changes may be associated with incipient cognitive decline. On the other hand, no clear associations have been observed between amyloid burden on PET using Pittsburgh Compound B (PET-PIB) and neurobehavioral changes in AD,<sup>94</sup> and studies have been inconclusive regarding relationships between the apolipoprotein E gene (APOE)  $\epsilon$ 4 carriers and agitation.<sup>95,96</sup>

Results of studies investigating associations between regional cortical volumes and agitation measures in AD using voxel-based morphometric MRI have been mixed. Some of these studies have shown that atrophy of the left frontal cortex, insula, and bilateral retrosplenial cortices is associated with agitation,<sup>97</sup> while disinhibition was more closely associated with gray matter volume reductions of the right subgenual cingulate gyrus AD of the right ventromedial prefrontal cortex.<sup>97</sup> Conversely, aberrant motor behavior in AD appears to be more closely associated with reduced gray matter volumes of the right basal ganglia, right dorsal anterior cingulate, and left premotor cortex.<sup>97</sup> Another study found associations between the agitation/aggression sub-scores of the NPI with right-sided posterior atrophy,<sup>98</sup> suggesting a predominantly right hemisphere influence on this emotional control measure. Similar right-sided predominance of hemispheric control of agitation was noted in studies using diffusion tensor imaging (DTI) in which associations of higher severity of agitation with fractional anisotropy reductions between the right frontotemporal and right parietal regions were observed.<sup>99</sup> It is notable that there is evidence that the severity of agitation may also be influenced by the degree of executive dysfunction or functional impairment, and that agitation results from an interaction between neuropathological substrates of emotional dysregulation and environmental stressors related to impaired task performance.

Impulsivity represents two distinct neuropsychiatric syndromes with identifiable neuroanatomical correlates, which result in the tendency to act prematurely in the absence of sufficient evidence to support the action or without full consideration of its possible adverse consequences.<sup>100</sup> The first construct includes aberrant processing of reward-processing and delay-discounting measures leading to risky decision making and “waiting” impulsivity. The second construct reflects abnormal response-inhibition and cognitive dysregulation, including “stopping” or “reflection” impulsivity.<sup>100,101</sup> The pathological substrates of the first construct include neuronal loss in subcortical structures, such as the striatal, thalamic, and subthalamic regions, which results in thalamocortical disinhibition, and subsequently, impaired reward-response mechanisms.<sup>102,103</sup> Neocortical pathology, particularly in the prefrontal cortex, influences decision-making, risk assessment, and action selection.<sup>104</sup> Based on these two distinct but interrelated pathways, impulsivity may be seen with

prefrontal or subcortical lesions; degeneration of the limbic ventral prefrontal cortex-striatal circuits is more likely to be associated with risky decision-making and intolerance to delays,<sup>105</sup> whereas impairment in dorsal motor or cognitive circuits, such as the inferior frontal gyrus or pre-supplementary motor area, is more likely to be associated with inability to refrain from or stop inappropriate actions.<sup>106</sup> Disruption of monoaminergic systems, particularly serotonin and noradrenaline, has been implicated in impulsivity.<sup>107</sup> Selective serotonin reuptake inhibitors (SSRIs) and noradrenergic agents (eg, atomoxetine) are commonly used to treat impulsivity due to neurodegenerative disorders including AD.<sup>108-110</sup> As the noradrenergic neurons of the locus coeruleus have been shown to be affected in the earliest symptomatic or pre-symptomatic stages of AD,<sup>111,112</sup> impulsivity may be an important indicator of early AD pathology in cognitively normal individuals.

## 6 | THE NEUROIMAGING OF AGITATION

In 2015 we reviewed the literature on neuroimaging and agitation in AD.<sup>113</sup> It was proposed that agitation in AD was associated with structural and functional deficits in a mix of brain regions associated with core AD neuropathology (particularly hippocampus and posterior cingulate cortex) as well as regions that may reflect other mechanisms (amygdala, insula, frontal, and anterior cingulate cortices). Newer data reinforce selected aspects of these hypotheses as reviewed below, adding new functional and neurochemical hypotheses as well. Several studies report an association of agitation in AD with volume loss in frontal cortex,<sup>97,114</sup> anterior cingulate cortex,<sup>114,115</sup> posterior cingulate cortex,<sup>97,114</sup> insula,<sup>97,114,115</sup> amygdala, and hippocampus.<sup>114</sup> There are two published functional imaging studies of agitation in AD. Hirono et al.<sup>90</sup> found that agitation in AD with hypoperfusion in left anterotemporal, right parietal, and bilateral dorsofrontal cortex using single-photon emission computerized tomography. Weissberger et al.<sup>116</sup> reported that an agitation factor of the NPI was associated with hypometabolism of right temporal, right frontal, and bilateral cingulate cortex. Among the individual items in the agitation factor, agitation was associated with cingulate hypometabolism, irritability with right frontal and insula hypometabolism, and both irritability and agitation with right temporal hypometabolism. There are two published studies of brain connectivity in agitated AD patients, one structural and one functional. Tighe et al.<sup>117</sup> reported that decreased functional anisotropy (presumably reflecting decreased white matter tract integrity) of the anterior cingulate was associated with agitation in AD. Ogama et al. examined a group of females with mild to moderate AD ( $n = 217$ ) and amnesic MCI (aMCI) and found both whole brain white matter hyperintensities and frontal lobe peri-ventricular hyperintensities to be associated with verbal aggressiveness.<sup>118</sup> Balthazar et al.<sup>119</sup> examined functional connectivity in 20 participants with mild to moderate AD using resting state fMRI. They reported that a hyperactivity factor score (including agitation) was associated with greater connectivity in the anterior regions of the right salience network (SN) including anterior cingulate and insula. Using fMRI to assess 169 participants with either AD or aMCI, Serra et al. showed an association between

symptoms of agitation, irritability, and disinhibition with ventral tegmental connectivity with the parahippocampal gyrus and cerebellar vermis.<sup>120</sup> There are two reports of neurochemical imaging of agitation in AD. Using MR spectroscopy, (Tsai et al.<sup>121</sup>) reported that agitation (measured with CMAI) correlated negatively with the NAA/Cr ratio in the left posterior cingulate gyrus ( $r = -0.46$ ;  $P = .02$ ). Sultzer et al.<sup>122</sup> imaged  $\alpha 4\beta 2$  nicotinic cholinergic receptor density using 2-[<sup>18</sup>F] fluoro-3-(2(S)azetidinylmethoxy)pyridine (2FA) PET and found that lower 2FA binding in anterior cingulate was strongly correlated with the Neurobehavioral Rating Scale agitation/disinhibition score.

Although these neuroimaging results using multiple modalities are somewhat disparate, they do point to some potential mechanisms. A number of findings point to the association of amygdala and SN function with agitation in AD. The amygdala (which is part of the SN) serves to signal emotionally salient external stimuli and contributes to the emotional awareness of an individual.<sup>123</sup> In this context, it is notable that Wright et al.<sup>124</sup> using task-based fMRI of viewing faces with varying emotions, reported increased amygdala activation in AD patients (compared to old and young controls) when viewing a sequence of faces expressing emotion, and that the intensity of this signal correlated with the severity of irritability and agitation. The anterior insula has been implicated in awareness of one's emotional state<sup>125</sup>; thus the abovementioned evidence of insular dysfunction in agitated AD patients suggests that they have deficits in monitoring their emotional state. Another possible mechanism comes out of the literature on brain mechanisms of anxiety disorders. As reviewed above, agitation in AD is associated dysfunction in frontal cortex, anterior cingulate cortex, orbitofrontal cortex, amygdala, and insula. These brain areas overlap with circuits that underlie inflated estimations of threat cost or probability, as well as maladaptive control of responses.<sup>126</sup> Agitation in AD may involve miscalculation of the magnitude of potential threats, accompanied by increased threat, attention and vigilance, and/or heightened reactivity to threat uncertainty. The patient is hyper-attentive to threat and also overestimating the severity of threat, resulting in emotional overreaction. In addition, agitation in AD is associated with progression of core AD neuropathology in the posterior cingulate cortex and hippocampus.

## 7 | THE NEUROIMAGING OF IMPULSIVITY

Impulsivity is a multifaceted behavior that includes behavioral disinhibition, risk-taking conduct, and impaired decision-making.<sup>127</sup> Although impulsivity is commonly reported in AD,<sup>128</sup> there have been few neuroimaging studies that specifically evaluate the neuroanatomical correlates of impulsivity in AD. This may be due to the NPI<sup>63</sup> being commonly used in most AD studies to measure NPS and impulsivity is not included in the sub-components of NPI, as it is framed as social disinhibition in this scale. However, very recently, Gill et al.<sup>129</sup> utilized traditional statistics and machine learning models to explore DTI and volumetric parameters in 203 participants from ADNI including those with normal cognition, MCI and AD, and MBI impulse dyscontrol derived from the NPI-Q using a published algorithm.<sup>57</sup> Linear



mixed-effects models identified impulse dyscontrol to be associated with increased mean axial and radial diffusivity in the cingulum, fornix, inferior/superior fronto-occipital fasciculus, and gray matter atrophy in parahippocampal gyrus and hippocampus, while machine learning selected nine features to predict presence of MBI ID. Although the cingulum and fornix were features consistent with those identified by conventional statistics, machine learning also identified the superior cerebellar peduncle, corpus callosum, supramarginal gyrus, and superior frontal regions, which may be targets for further exploration. On the other hand, there have been various neuroimaging studies of impulsivity in PD, as ICD is a common neuropsychiatric complication of PD. Therefore, we will review the neuroimaging studies of impulsivity in PD to elucidate the structural, functional and metabolic correlates of impulsivity.

There have been inconsistent findings regarding cortical thickness in PD patients with impulsivity. Significant cortical thinning in the fronto-striatal circuits, specifically in the right superior orbitofrontal, left rostral middle frontal, bilateral caudal middle frontal region, and corpus callosum; and volume reduction in the right accumbens and concomitant increased volume in the left amygdala have been reported in PD patients with ICD.<sup>130</sup> Furthermore, a recent study shows that PD patients with impulsive-compulsive behaviors (ICBs) have cortical thinning in the left precentral and superior frontal regions.<sup>131</sup> However, another study reports an increase in cortical thickness in the anterior cingulate and orbitofrontal cortices in PD patients with ICD,<sup>132</sup> while one other study demonstrates no difference in gray matter volume between PD patients with and without ICD.<sup>133</sup> In the same study, an increased connectivity within the salience and default-mode networks and a decreased connectivity within the central executive network is found to be associated with ICD in PD.<sup>133</sup> Another resting-state functional study found that PD patients with ICB compared to those without ICB, are associated with altered connectivity between the left anterior putamen, left inferior temporal gyrus, and left anterior cingulate gyrus,<sup>134</sup> while in a recent study, the severity and duration of PD-ICB in PD is shown to modulate the functional connectivity between sensorimotor, visual, and cognitive networks.<sup>131</sup> A FDG-PET study further shows that PD patients with higher impulsivity scores have higher metabolism in the orbitofrontal cortex, anterior cingulate cortex, and right insula.<sup>135</sup>

Current evidence has consistently shown that impulsivity is associated with brain dysfunction involving the frontal-striatal and mesolimbic regions. The dorsolateral and medial prefrontal cortices, including the orbitofrontal cortex, anterior cingulate cortex, and the ventral striatum, have been reported to play an important role in impulsive behaviors due to abnormal emotions, decision-making, and impulse control,<sup>136</sup> whereas the amygdala plays a key role in associating sensory cues with their motivational and emotional significance.

## 8 | BIOMARKERS OF NPS

The pathogenesis of NPS in neurodegenerative disorders is not entirely clear, although several different hypotheses have been

proposed. To increase our knowledge of the different proposed mechanisms associated with the presence of NPS different biomarkers such as blood, plasma, and cerebrospinal fluid (CSF) might be studied through analytic genomics, proteomics, and lipidomics techniques. Potential markers include: AD markers (tau, phosphorylated tau (P-tau), and amyloid beta(A $\beta$ )1-42, 38, and 40); cholinergic markers (acetylcholinesterase (AChE), butyrylcholinesterase (BChE)); serotonergic markers (5-hydroxytryptamine (5-HT), 5-hydroxyindoleacetic acid (5-HIAA)); noradrenergic (noradrenaline (NA), 3-methoxy-4-hydroxyphenylglycol (MHPG)); dopaminergic (dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 3-methoxytyramine (3-MT)); neuroinflammation (cytokines, glycoprotein YKL-40); synaptic damage markers (neurogranin); axonal damage markers (neurofilament); and neurotrophic factors (brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), S100 calcium-binding protein B (S100B)).

Ruthirakuhan et al. recently conducted a systematic review focused on the biomarkers of agitation and aggression in AD. They found that the associations between apolipoprotein E(APOE)  $\epsilon$ 4 carrier status and agitation and aggression in AD have been largely inconsistent.<sup>137</sup> One retrospective study found that the hazard of developing AD for APOE  $\epsilon$ 4 carriers was significantly higher for those with baseline agitation.<sup>138</sup> Another study showed a higher frequency of APOE  $\epsilon$ 4 carrier status in patients with AD who have agitation.<sup>139</sup> One genetic study found no associations of APOE  $\epsilon$ 4 carrier status with agitation, but demonstrated mild associations of suppressed frontally mediated behaviors in AD with genotypes that lead to boosted angiotensin-converting enzyme levels and activity, or with lipid metabolism genotypes related to improved myelin biosynthesis in the brain.<sup>140</sup> Another genetic study found associations of the T allele of the 3' untranslated region of prion-like protein gene (*PRND*) polymorphism with an increased cumulative behavioral load and an elevated risk for delusions, anxiety, agitation, apathy and irritability for patients with AD, but not for patients with MCI, and for no patient group regarding APOE  $\epsilon$ 4 carrier status.<sup>141</sup>

The strongest evidence for the role of agitation and impulsivity in mid and late life over further development or progression of dementia has come from longitudinal studies. Whereas most prospective cohorts have employed essentially clinical measures of patient evaluation in longitudinal clinical and epidemiological studies,<sup>5,14,20,38,128,142-153</sup> some studies have correlated neuroanatomical parameters<sup>114,154</sup> and biomarkers of amyloidogenesis<sup>155</sup> with NPS. Bloniecek et al. found that in a cohort of subjects with AD and NPS agitation measured with the Cohen-Mansfield Agitation Inventory (CMAI) correlated with total-tau ( $r = 0.36$ ,  $P = .04$ ) and phosphorylated-tau  $r = 0.35$ ,  $P = .05$ ) in AD patients, indicating that tau-mediated pathology including neurofibrillary tangles and the disease intensity might be associated with agitation in AD.<sup>156,157</sup> In their systematic review of CSF correlates of NPS in AD and aMCI, Showraki et al. found that all studies that met inclusion criteria and examined the relationship of Core AD CSF biomarkers (Low A $\beta$ 42, elevated tau, etc.) with the agitation/aggression domain of NPS, demonstrated a significant relationship between Core AD CSF biomarkers and the agitation/aggression domain.<sup>158</sup>

The serotonin system may play a role in the development of NPS in MCI. In 2017, Smith et al., using the radiotracer [11C]-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-enonitrile ([11C]-DASB), showed that as compared to normal controls, participants with MCI had fewer serotonin transporters in the cortical and limbic regions of the brain. MCI participants in this study had NPS in the mild range, which was significantly higher than in normal controls.<sup>159</sup> Measured serotonin transporters act as a more specific marker of serotonin terminals and serotonin projection integrity than serotonin receptors 1A or 2A.<sup>160</sup> Yet, it remains unclear how these decreases in serotonin transporters in MCI participants relate to the emergence of NPS.

The relationship between cytokines, neuroinflammation, and NPS in AD is complex and not entirely elucidated at this point. Holmgren et al. analyzed the relationships between NPS in dementia and CSF levels of cytokines including: interleukin(IL)-6, tumor necrosis factor (TNF)- $\alpha$ , IL-10, and cytokine receptor soluble form IL-1RII. The 95 subjects analyzed in this study included patients with MCI, AD, VasD, and AD and vascular mixed dementia. All subjects scored  $\geq 10$  on the NPI total score.<sup>161</sup> Levels of the anti-inflammatory cytokine, IL-10, correlated inversely with the NPI total score ( $P = .004$ ), the NPI sub-scores of agitation ( $P = .009$ ), and night time behaviors ( $P = .01$ ) and trended toward an inverse correlation with depression ( $P = .09$ ). TNF- $\alpha$  CSF levels were undetectable and IL-6 CSF levels did not show any correlations with NPS.<sup>161</sup>

Using a sickness behavior paradigm, Holmes et al. examined the relationships between NPS and serum levels of pro-inflammatory cytokines TNF- $\alpha$ , IL-6, and C-reactive protein (CRP) in a cohort of 275 subjects with either possible or probable AD over a 6-month time span.<sup>162</sup> Sickness behaviors refer to a set of behavioral symptoms, such as depression, anxiety, and apathy, that occur during the course of systematic inflammation and which may serve adaptive purposes. A total of 222 subjects had complete clinical and serum inflammatory marker data at 6-month follow-up. Subjects with low TNF- $\alpha$  serum levels throughout the 6 months had lower NPI total scores as compared to subjects with high TNF- $\alpha$  serum levels. The high TNF- $\alpha$  serum level group had significantly higher frequencies of agitation ( $P = .02$ ), depression/dysphoria ( $P = .008$ ), and anxiety ( $P = .01$ ). There were no statistically significant differences in agitation between the high and low quartiles for IL-6 and the high and low quartiles for CRP, although the high versus low IL-6 quartiles did have more frequent hallucinations ( $P = .015$ ) and apathy ( $P = .003$ ).<sup>162</sup>

A study of 16 AD patients and 16 normal controls conducted in Japan examined the relationships between agitation, circadian rhythms of behavior, and serum levels of cortisol, IL-1 $\beta$  and Natural Killer Cell Activity (NKCA) over 1 year. The 16 subjects were categorized into stages of stable, pre-agitation, and agitation. When comparing AD subjects in the stable stage to AD subjects in the agitation stage, there was a statistically significant increase in serum cortisol and IL-1 $\beta$  and decrease in NKCA.<sup>163</sup>

A recent clinical trial with nabilone as a treatment for agitation in AD examined biomarker changes associated with treatment response in 38 subjects. The double-blinded, 14-week-long, cross-over, randomized, placebo-controlled trial included 6 weeks in the drug phase and 6

weeks in the placebo phase, with a 1-week washout period. Even after adjusting for cognition, serum levels of the pro-inflammatory cytokine TNF- $\alpha$  correlated with agitation severity ( $P = .04$ ). During the nabilone treatment phase, a lower baseline TNF- $\alpha$  serum level demonstrated an association with decreases in agitation severity. Decreases in TNF- $\alpha$  were also associated with decreases in agitation severity.<sup>164</sup>

In total these studies suggest that several pro-inflammatory cytokines levels directly correlate with agitation frequency<sup>161,162</sup> and severity,<sup>163,164</sup> while anti-inflammatory cytokine levels inversely correlate with agitation,<sup>161</sup> and agitation treatment response to nabilone correlates with decreases in TNF- $\alpha$ <sup>164</sup> (See Figure 2). It should be noted that most of the biomarker work that has been done in NPS focuses on people with dementia or at high risk of converting to dementia within 5 years. Understanding earlier cytokine and other biomarker changes associated with agitation and impulsivity remains an important research question that has not yet been fully answered.

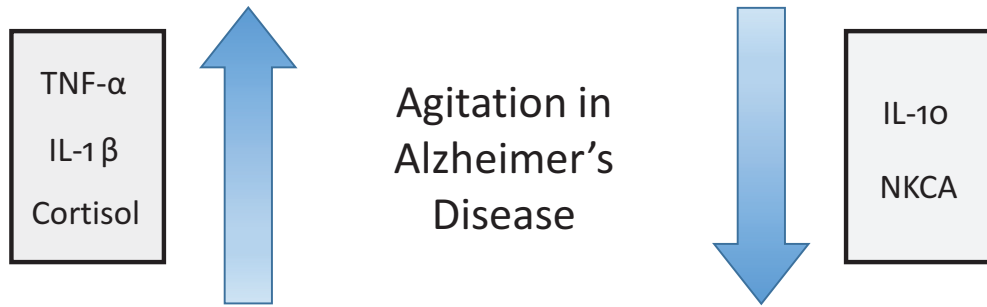
## 9 | COURSE AND PROGNOSIS

There has been growing evidence in the literature that agitation and impulsivity in mid and late life may be risk markers for progression to dementia in later years. Most longitudinal studies discuss the progression of MCI to AD or to another dementia without discussion of etiology. For the most part, studies regarding agitation and impulsivity in other neurodegenerative diseases (such as FTD or DLB) have been either cross-sectional studies or studies focused on patient populations with NPS who already meet criteria for major neurocognitive disorder or dementia.

Most studies were conducted before the provisional consensus clinical and research definition of agitation in cognitive disorders elaborated by members of the IPA<sup>35</sup> or the ISTAART research diagnostic criteria for MBI,<sup>26</sup> thus compromising generalizability. Overall, they do not mention whether agitation impaired interpersonal relationships or the ability to participate in activities of daily living. The instruments that were employed for evaluation of agitation and impulsivity were highly variable across studies, although most of them included assessment of the agitation/aggression domain of the NPI (as discussed previously).<sup>63</sup>

A few cross-sectional studies were able to measure the progression of agitation by dementia stage in late-onset AD,<sup>140,165,166</sup> early onset AD,<sup>167,168</sup> or group comparisons of MCI versus dementia<sup>65,169,170</sup> or MCI versus older cognitively unimpaired people.<sup>39</sup> One cross-sectional study also showed that intensity of agitation correlates with CSF biomarkers of neurodegeneration in patients with AD, but not in patients with VasD or mixed dementia<sup>157</sup>; the same may be true for patients with MCI.<sup>171</sup> The severity of dementia is associated with increased intensity of aggressive behavior both in nursing home patients<sup>172</sup> and in community-dwelling patients.<sup>173</sup>

One cross-sectional study showed that agitation was non-significantly less frequent and less intense in PD dementia than in late-onset AD or in DLB.<sup>174</sup> Regarding primary progressive aphasia, one retrospective study showed that patients with semantic primary



**FIGURE 2** Cytokine, Neuroendocrine and Immune System Associations with Agitation in Alzheimer's Disease

progressive aphasia developed more frequent and intense agitation than patients with non-fluent primary progressive aphasia, unrelated to length of the neurodegenerative disease.<sup>175</sup>

Most of the data on the effects of agitation, aggression, and impulsivity have come from longitudinal studies of patients with diagnosed AD. There is consistent evidence that the presence of one or more of these symptoms, as well as delusions and hallucinations as psychotic features, is associated with an increased likelihood of greater cognitive decline, admission to nursing homes, and mortality.<sup>148,150,153</sup> There is initial evidence that the presence of mild behavioral symptoms that may not reach the threshold of agitation/aggression or impulsivity is associated with the development of dementia in older adults.<sup>81</sup> It remains unclear if the presence of agitation or impulsivity in cognitively intact older adults is also a precursor to dementia, and there is evidence that these symptoms rarely occur when patients first present with memory complaints for a diagnostic evaluation.<sup>176</sup> A recent prospective study of 96 subjects with MCI conducted in France for 4 years demonstrated the presence of agitation/aggression as a risk factor for conversion to dementia (hazard ratio [HR] 3.9 confidence interval [CI] 1.9-8.2).<sup>177</sup>

It is expected that long-term studies starting in mid-life, preferably incorporating neuroimaging and biofluid-based biomarkers, might bring further evidence on the role of agitation and impulsivity as risk markers for neurocognitive disorders in later years.

## 10 | TREATMENT OF AGITATION AND IMPULSIVITY IN PRE-DEMENTIA SYNDROMES

Of the publications included in this review, we did not find any studies specifically addressing the treatment of agitation and impulsivity in patients with cognitive impairment without dementia and/or pre-dementia syndromes that do not include cognitive impairment. Although, there is a significant body of evidence regarding treatment of agitation and impulsivity in patients with AD, FTD, DLB, and PD, one cannot extrapolate and assume that these treatments will be effective in the cognitive impairment no dementia, or pre-dementia syndromes. We review current treatments of agitation and impulsivity in the dementia population to inform potential future treatments in pre-dementia syndromes. This is not an endorsement or recom-

mendation of applying these treatments to those with pre-dementia syndromes. Clinical trials need to be conducted to test and prove that behavioral and pharmacologic treatments in pre-dementia populations can effectively improve agitation and impulse dyscontrol.

In patients with AD, behavioral interventions are recommended as first-line interventions and are supported by high quality evidence.<sup>178-181</sup> Specifically the interventions focusing on improving communications, individualized care, interventions to support caregivers, music therapy, and dementia care mapping have shown efficacy in this population.<sup>180</sup> Among medications, the antipsychotic medications have the most direct evidence for treatment of agitation and aggression in dementia with multiple RCTs supporting their efficacy.<sup>182-189</sup> However these medications are associated with several adverse effects such as extrapyramidal symptoms, metabolic syndrome, stroke, falls, and an increased risk of death.<sup>183,190</sup> Nevertheless these medications are used widely for this indication, particularly in patients with severe agitation and aggression.<sup>191-194</sup> There is also evidence for use of citalopram for treating agitation in patients with AD.<sup>110,195-197</sup> A recent large multicenter RCT has shown efficacy of citalopram in treating agitation in patients with AD and mild to moderate degree of cognitive impairment, but concerns were raised about QTc interval prolongation and cognitive decline with drug versus placebo.<sup>110,198</sup> Further analysis of data from this trial revealed that the S-citalopram enantiomer was responsible for most of the benefits, whereas the R-citalopram enantiomer was responsible for most of the adverse effects such as cognitive decline and QT interval prolongation.<sup>199</sup> Other agents that have shown efficacy in this population are anticonvulsants with carbamazepine having RCT level evidence.<sup>200,201</sup> Valproic acid showed some favorable results in open label trials but these findings were not replicated in RCTs where there was a clear lack of benefit and a high rate of adverse events, and thus it is not recommended for use in this population.<sup>202</sup> In addition, when used to treat people with dementia, retrospective evidence suggests that valproic acid has an increased mortality rate, comparable to some antipsychotics and possibly higher than the atypical antipsychotic quetiapine.<sup>203</sup> Studies in patients with FTD have shown good quality evidence for trazodone followed by SSRIs for treatment of agitation and impulsivity, and these medications are favored over antipsychotics in this population.<sup>204-207</sup> Antipsychotics are still recommended for more severe cases with agitation and aggression that pose a safety risk.<sup>204</sup> Cholinesterase inhibitors have been shown to worsen agitation

**TABLE 1** Representative studies on the course of agitation and impulsivity as risk markers for neurocognitive disorders

References	Study design	n	Endpoints	Findings
Donovan et al., 2018 <sup>155</sup>	Prospective	270	Pittsburgh compound B PET measures of cortical aggregate A $\beta$ , depression measures, and depressive symptom clusters in cognitively healthy older adults.	Higher A $\beta$ burden was associated with increasing anxious-depressive symptoms over time in cognitively healthy older adults, supporting the hypothesis that emerging neuropsychiatric symptoms represent an early manifestation of preclinical Alzheimer's disease
Oliveira et al., 2017 <sup>140</sup>	Cross-sectional	201	Cerebrovascular metabolism genotypes, NPS in late-onset AD	Agitation frequency and severity increased with increasing severity of AD, Mild AD (50.0%), Mod AD (63.0%), and Sev AD (74.2%)
Burke et al., 2016 <sup>138</sup>	Retrospective	11,453	Survival analyses between NPS, APOE $\epsilon$ 4 carrier status, and progression to AD in cognitively healthy adults	Hazard of AD development for APOE $\epsilon$ 4 carriers was approx 13X higher for patients with delusions and 11X higher for those with apathy and disinhibition. Also greater rates for those with hallucinations, agitation, depression, and anxiety
Forrester et al., 2016 <sup>146</sup>	Prospective	540	Clusters of NPS in patients with incident MCI and risk of conversion to dementia	Most patients who progressed to dementia had aMCI at baseline, whereas patients with the severe NPS cluster (agitation, anxiety, apathy, night-time behaviors, disinhibition) had the highest hazard of progression to dementia (2.69)
Gómez-Tortosa et al., 2016 <sup>175</sup>	Retrospective	80	Prevalence of agitation in semantic PPA and non-fluent PPA, and clinical variables	Patients with semantic PPA developed more frequent and intense agitation, with greater need for anti-psychotics than patients with non-fluent PPA. Agitation was only associated with delusions and hallucinations.
Oliveira et al., 2015 <sup>174</sup>	Cross-sectional	78	Differentiation of DLB from PDD by way of NPS, as well as behavioral contrasts between patients with DLB syndromes paired with APOE $\epsilon$ 3/ $\epsilon$ 3 carriers with LOAD	Agitation prevalence varied by group: PDD (28.6%), DLB (52.0%), and APOE $\epsilon$ 3/ $\epsilon$ 3 carriers with LOAD (59.0%)
Pankratz et al., 2015 <sup>149</sup>	Prospective	1,449	Development of a risk score for incident MCI, including NPS as measured by the NPI.	Baseline agitation significantly increased the risk of conversion to MCI
Peters et al., 2015 <sup>5</sup>	Prospective	335	Examination of the relationship between clinically significant NPS in mild AD and progression to severe dementia or death	Almost 20% of all patients with incident AD developed severe dementia, with more rapid progression associated with agitation and psychosis, features that also predicted earlier death
Pink et al., 2015 <sup>14</sup>	Prospective	332	A population-based study that assessed the interaction between APOE $\epsilon$ 4 carrier status, NPS, and the risk of incident dementia among subjects with MCI	Hazard ratios for conversion from MCI to dementia were significant regarding baseline agitation (1.97), night-time behaviors (1.68), depression (1.63), and apathy (1.62), regardless of APOE haplotypes
Ringman et al., 2015 <sup>167</sup>	Cross-sectional	261	Characterization of NPS in people without dementia who carried autosomal dominant AD mutations with non-carriers	Depression, apathy, disinhibition, irritability, sleep changes and agitation were more common and the degree of self-rated depression more severe in mildly symptomatic mutation carriers relative to non-carriers. Lower rates of depressive symptoms were found in cognitively asymptomatic mutation carriers
Rockwood et al., 2015 <sup>170</sup>	Cross-sectional	1,072	Assessment of frequency of NPS in relation to dementia severity, as well as specific clusters of NPS	Agitation was the most common NPS, present in 37% of all patients, whereas decreased initiative was related to aggression in moderate and severe dementia
Rosenberg et al., 2015 <sup>113</sup>	Clinical trial (placebo arm)	92	Changes in agitation in the placebo arm of the CitAD study	Patients with AD who received placebo and a psychosocial intervention over 9 weeks had improvements in agitation scores, cognition and function, possibly due to regression to the mean, response to the intervention, natural course of symptoms, or nonspecific benefits of participation in a trial

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**TABLE 1** (Continued)

References	Study design	n	Endpoints	Findings
Tanaka et al., 2015 <sup>168</sup>	Cross-sectional	92	Investigated the relationship between dementia severity and NPS in early onset AD	Agitation, apathy, disinhibition, irritability, and aberrant motor behavior worsened with dementia severity in early onset AD, whereas delusions, depression, and anxiety remained stable
Zahodne et al., 2015 <sup>153</sup>	Prospective	517	Characterization of the relationships between agitation and cognition or dependence in patients with probable Alzheimer's disease	Rates of increase in agitation separately correlated with rates of decline in both cognition and independence
Bloniecki et al., 2014 <sup>157</sup>	Cross-sectional	95	Examination of the association between agitation and cerebrospinal fluid amyloid beta 1-42, total <i>tau</i> and phospho- <i>tau</i> in patients with AD, vascular dementia, or mixed dementia who had behavioral disturbances	Intensity of agitation correlated with cerebrospinal fluid total <i>tau</i> and phospho- <i>tau</i> in patients with AD, but not in patients with vascular dementia or mixed dementia
De Oliveira et al., 2014 <sup>165</sup>	Cross-sectional	217	Evaluation of the prevalence of agitation according to the stage of AD, as well as of correlations of pharmacological treatment with stage-specific NPS	Agitation was more frequent and more severe with increasing severity of AD, affecting 51.8% of mildly impaired patients, 65.4% of moderately impaired patients, and 70.0% of severely impaired patients, whereas cholinesterase inhibitors and anti-psychotics (but not anti-epileptic drugs) were associated with more agitation for moderately impaired patients, probably reflecting the need for more psychotropic therapy
Geda et al., 2014 <sup>20</sup>	Prospective	1,587	Estimation of the risk of incident MCI in cognitively unimpaired older people according to baseline NPS	Baseline agitation, apathy, anxiety, irritability and depression increased the risk for later MCI, while euphoria, disinhibition, and night-time behaviors predicted non-amnesic MCI only
Selbæk et al., 2013 <sup>151</sup>	Prospective	931	Investigation of the course of NPS in nursing home patients with dementia over 53 months	Agitation, irritability, disinhibition and apathy were the most prevalent and persistent symptoms, and increased in severity according to the severity of dementia
Ramakers et al., 2013 <sup>171</sup>	Cross-sectional	268	Investigation of associations of CSF concentrations of amyloid beta 1-42 and total <i>tau</i> with NPS in patients with MCI	Anxiety was associated with abnormal CSF concentrations of $A\beta$ 1-42 and total <i>tau</i> , while agitation and irritability were associated with abnormal CSF concentrations of $A\beta$ 1-42 only.
Trzepacz et al., 2013 <sup>66</sup>	Prospective	462	Characterization of neuroimaging parameters associated with agitation in patients with probable AD, stable patients with MCI, and patients with MCI converting to AD	Agitation worsened in patients with probable AD and in patients with MCI converting to AD, whereas severity of agitation was associated with greater atrophy of the anterior salience network (frontal, insular, amygdala, cingulate, and hippocampal regions of interest), uncorrelated with APOE $\epsilon$ 4 carrier status
Van der Mussele et al., 2013 <sup>65</sup>	Cross-sectional	780	Characterization of behavior in MCI, AD, and cognitively healthy adults	The prevalence and severity of agitation in MCI was intermediate between normal aging and AD
Bettney et al., 2012 <sup>143</sup>	Prospective	84	Investigation of the stability of neuropsychiatric sub-syndromes with progression of vascular dementia and AD	The most stable group of symptoms included delusions, hallucinations, irritability and agitation, with evidence of some stability particularly during the later stages of dementia
Bidzan et al., 2012 <sup>128</sup>	Prospective	31	Assessment of the relationship between agitation and impulsivity and cognitive function in nursing home patients with AD	Worse cognitive function was associated with greater intensity of agitation and impulsivity, but the progression of such behaviors was decreased by neuroleptics and mood stabilizers
Brody et al., 2012 <sup>144</sup>	Prospective	873	Evaluation of cognitive decline in 2 years according to NPS in community-dwelling older people with no diagnosis of dementia	Baseline agitation and apathy were associated with diagnosis of MCI, whereas depression, agitation, anxiety and apathy were associated with impairment in at least one cognitive domain, but only anxiety and agitation were significantly associated with cognitive decline

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**TABLE 1** (Continued)

References	Study design	n	Endpoints	Findings
Flirski et al., 2012 <sup>141</sup>	Cross-sectional	147	Assessment of associations between <i>APOE</i> , <i>CYP46</i> , <i>PRNP</i> , and <i>PRND</i> polymorphisms and the neuropsychiatric profile of patients with MCI and AD	The T allele of the 3' untranslated region of <i>PRND</i> polymorphism was associated with increased risks for delusions, anxiety, agitation, apathy and irritability only for patients with AD
Majic et al., 2012 <sup>172</sup>	Cross-sectional	304	Investigation of the relationship between dementia severity, age, gender, prescription of psychotropics, and agitation in nursing home patients with dementia	Dementia severity predicted higher risk for agitation and depression, whereas the severity of depression was associated with physically and verbally aggressive behaviors, indicating that, in severe dementia, depression in some patients might underlie aggressive behavior
Wadsworth et al., 2012 <sup>152</sup>	Prospective	812	Investigation of the relationship between neuropsychiatric symptoms and global functional impairment at baseline and over 3 years in cognitively healthy older people, patients with MCI, and patients with mild AD	Increased baseline hallucinations, anxiety and apathy (but not agitation) were associated with greater global functional impairment at baseline, whereas the presence of hallucinations and apathy at baseline (but not agitation) was associated with greater global functional impairment over time across all participants
Josephs Jr et al., 2011 <sup>154</sup>	Prospective	86	Determination of baseline clinical characteristics, including anatomical subtype, that could predict functional decline in behavioral variant frontotemporal dementia	Faster rates of functional decline were observed in the frontal dominant and frontotemporal subtypes of behavioral variant frontotemporal dementia, whereas participants with less agitation, disinhibition, and night-time behaviors at presentation showed faster functional decline as well
Spalletta et al., 2010 <sup>166</sup>	Cross-sectional	1,015	Investigation of the relationship between specific NPS and severity of AD	Agitation had an increased occurrence with increasing severity of untreated AD, reaching clinical significance in more than one quarter of severe dementia patients
Geda et al., 2008 <sup>39</sup>	Cross-sectional	1,909	Estimation of the prevalence of NPS in MCI and cognitively unimpaired older people in a population-based study	The most distinguishing features between the groups, all of them more frequent in patients with MCI, were apathy, agitation, anxiety, irritability and depression, whereas apathy, agitation and irritability were more prevalent in amnesic MCI than in non-amnesic MCI
Scarmeas et al., 2007 <sup>150</sup>	Prospective	497	Investigation of the presence of disruptive behavior (wandering, agitation, aggression, sundowning) and its predictive value for decline in cognition decline in function, institutionalization and mortality for patients with mild AD	Sundowning was associated with faster cognitive decline, wandering with faster functional decline and institutionalization, and agitation with faster cognitive and functional decline, whereas disruptive behavior was not associated with mortality
Craig et al., 2004 <sup>139</sup>	Cross-sectional	400	Association of agitation with <i>APOE</i> haplotypes in moderate to severe AD	Higher frequency of <i>APOE</i> $\epsilon$ 4 carriers among patients with agitation, also noted when <i>APOE</i> $\epsilon$ 4 carriers were compared against <i>APOE</i> $\epsilon$ 4 non-carriers
Chan et al., 2003 <sup>169</sup>	Cross-sectional	454	Comparisons of prevalent NPS in community-dwelling older people with dementia or MCI	Compared to patients with dementia, those with MCI had lower prevalence of any NPS (psychosis, depression, or agitation), and particularly of agitation
Copeland et al., 2003 <sup>38</sup>	Prospective	144	Assessment of the impact of cognition on functional abilities and NPS over 3 years to determine who had functional decline and who developed AD	Particular types of personality change, such as agitation and passivity, but not depressive symptoms, were related to functional decline
Lopez et al., 1999 <sup>148</sup>	Prospective	179	Examination of whether use of psychiatric medication and the presence of abnormal behaviors affect progression of AD	Use of anti-psychotics was associated with functional decline. Use of hypnotics was associated with death. Psychosis and agitation predicted functional decline even when use of psychiatric medication was taken into account
Devanand et al., 1997 <sup>145</sup>	Prospective	235	Development and persistence of psychopathologic symptoms in patients with AD	Agitation was prevalent at least once in 62.2% of patients and persisted in most of them along 3 years of follow-up, with almost 50% increase in prevalence throughout the study

(Continues)

**TABLE 1** (Continued)

References	Study design	n	Endpoints	Findings
Levy et al., 1996 <sup>147</sup>	Prospective	181	Recurrence of agitation in 1 year in patients with AD	Recurrence rates of agitation at one year reached 93% and were associated with more rapid functional decline. Recurrences were greater in patients who had multiple NPS and in women
Hamel et al., 1990 <sup>173</sup>	Cross-sectional	213	Assessment of predictors and consequences of aggressive behavior by community-dwelling patients with dementia	Aggression was reported in 57.2% of patients, predicted by greater frequency of behavior and memory problems, premorbid aggression, and a more troubled premorbid social relationship between patient and caregiver, whereas patient aggression predicted the decision to discontinue home care

and impulsivity in FTD and are thus avoided in this population.<sup>207</sup> In contrast, in patients with DLB, cholinesterase inhibitors may improve NPS, including agitation and impulsivity, and may be used as first-line agents.<sup>208</sup> Antipsychotic medication use is relatively contraindicated in DLB as it can precipitate severe extrapyramidal symptoms; however, there is evidence to support the use of clozapine and quetiapine (weaker evidence) in small doses.<sup>209,210</sup> In patients with PD, impulsivity is associated with dopamine agonists in a significant proportion of cases and may respond to dopamine agonist dose reduction.<sup>211,212</sup> Empirical use of other agents such as cholinesterase inhibitors, antipsychotics, antidepressants, and mood stabilizer medications is also reported.<sup>212</sup> The use of deep brain stimulation for impulsivity related to PD is controversial.<sup>213</sup> Some studies provide support for the use of electroconvulsive therapy for NPS of dementia, particularly in patients with treatment refractory illness but it is an invasive procedure associated with several risks including cognitive adverse effects.<sup>214,215</sup> There is no evidence for or against other non-invasive brain stimulation interventions such as transcranial magnetic stimulation or transcranial electrical stimulation for treatment of agitation or impulsivity in cognitive disorders.

Ongoing clinical trials may also help clarify which pharmacotherapeutic treatments may be suitable for pre-dementia populations. These include studies of: (1) escitalopram (NCT03108846)<sup>216</sup>; (2) mirtazapine (NCT03031184)<sup>217</sup>; (3) cannabinoids (NCT04075435, NCT02792257)<sup>218,219</sup>; (4) prazosin (NCT03710642)<sup>220</sup>; (5) brexpiprazole (NCT03548584)<sup>221</sup>; (6) dextromethorphan-quinidine (NCT03393520)<sup>222</sup>; and (7) lithium (NCT02129348),<sup>223</sup> among others.

## 11 | CONCLUSION

This review highlights a gap in the literature regarding agitation and impulsivity (part of the MBI domain of impulse dyscontrol) and the role they play as risk factors for incident cognitive decline and dementia. Numerous studies show that in general, NPS predict progression from normal cognition and MCI to dementia. A smaller body of evidence suggests that this is true for agitation and impulsivity as well. Yet, there are significant limitations with the current literature base. First, nearly all scales used to study agitation and impulsivity in pre-dementia

populations were designed and validated for populations with dementia or major neurocognitive disorder, rather than for patients with normal cognition or MCI. Ongoing validation studies for the MBI-C seek to address this first gap. A second problem with the literature is that most epidemiologic, biomarker, longitudinal, and treatment studies took place prior to creation of the IPA agitation in cognitive disorders criteria and the ISTAART MBI research diagnostic criteria. Variation in nomenclature and definitions complicate interpretations of study results. In addition, unlike in agitation, there is no current international consensus definition or criteria for impulsivity, making the symptom more difficult to effectively study and treat. This contributes to impulsivity in normal cognition and MCI populations being understudied as an NPS as compared to agitation. Next, more work needs to be done to describe the biomarkers associated with the impulse dyscontrol subdomain of MBI. Furthermore, prevalence of agitation and impulsivity vary widely according to study. This may be a reflection of pre-dementia syndromes with different underlying etiologies being grouped together. Finally, treatment studies are largely extrapolations from studies that focus on mixed populations of MCI and dementia, or dementia alone.

From review of the existing evidence in similar disorders we make the following recommendations around treatment of agitation and impulsivity in pre-dementia syndromes. First, the etiology of agitation and impulsivity and the underlying condition leading to these symptoms should be determined with appropriate clinical workup. This is important, as the treatment is likely to vary depending on underlying etiology, which could range from a medical cause such as delirium or TBI, pre-existing psychiatric condition, substance use, and late-onset primary psychiatric disorder, to early manifestations of a neurodegenerative disorder. Second, iatrogenic causes such as dopamine agonist-induced agitation and impulsivity and antipsychotic induced akathisia should be addressed. Third, we are unable to recommend non-pharmacologic or pharmacologic interventions at this time, because the studies have not been done and there is not sufficient evidence to make such a recommendation at this time. Fourth, future studies should examine the risks and benefits of non-pharmacologic and pharmacologic (antidepressant, antipsychotic, mood stabilizer, and others) interventions that have been found to be effective in treatment of agitation and impulsivity in dementia. It needs to be determined if treatment of later-life emergent and sustained NPS in

pre-dementia populations will change the disease course and delay or prevent incident cognitive decline and dementia. Similarly, studies are also required using dementia disease-modifying drugs in MBI NPS to determine their role in disease course modification. Finally, efforts should be made to explore the role of non-invasive brain stimulation to develop novel biomarkers and targeted treatment interventions for patients with agitation and impulsivity in pre-dementia syndromes, as an alternative to pharmacological interventions, which are the mainstay of current treatment.

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## CONFLICTS OF INTEREST

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### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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