**RESEARCH ARTICLE**

# Detecting Non-cognitive Features of Prodromal Neurodegenerative Diseases

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**Abstract:** **Background**: Prodromal Neurodegenerative Disease (ND) due to tauopathies such as Alzheimer's Disease (AD) and Synucleinopathies (SN) such as Parkinson's Disease (PD) and Dementia with Lewy Bodies (DLB) present subtly. Although ND are considered cognitive disorders, in fact ND present with behavioral and even medical symptomatology years to decades prior to the onset of cognitive changes. Recognizing prodromal ND syndromes is a public health priority because ND is common, disabling and expensive. Diagnosing prodromal ND in real world clinical settings is challenging because ND of the same pathology can present with different symptoms in different people. Individual variability in nature and variability in nurture across the life course influence how ND pathology manifests clinically. The objective of this study was to describe how non-cognitive symptoms from behavioral, medical, neurological and psychiatric domains cluster in prodromal and early stages of ND.

***Methods***: This was an observational study of patients receiving routine clinical care for memory disorders. All patients receiving a standardized evaluation including complete neurological history and examination and standardized brief neuropsychological testing. A Principal Component Analysis (PCA) considering emotion, motor, sensory and sleep factors was performed on the entire sample of patients in order to identify co-occurring symptom clusters. All patients received a consensus diagnosis adjudicated by at least two dementia experts. Patients were grouped into Cognitively Normal, Detectable Cognitive Impairment, and Mild Cognitive Impairment categories due to AD and/or PD/LBD or NOS pathology. Symptom cluster scores were compared between clinical diagnostic groups.

***Results***: In this study 165 patients completed baseline neuropsychological testing and reported subjective measures of non-cognitive symptoms. Four syndrome specific symptom factors emerged and eight non-specific symptom factors. Symptoms of personality changes, paranoia, hallucinations, cravings, agitation, and changes in appetite grouped together into a cluster consistent with an "SN Non-motor Phenotype". Appetite, walking, balance, hearing, increased falls, and dandruff grouped together into a cluster consistent with an "SN Motor Phenotype". The Prodromal AD phenotype included symptoms of anxiety, irritability, apathy, sleep disturbance and social isolation. The fourth factor included symptoms of increased sweating, twitching, and tremor grouped into a cluster consistent with an Autonomic phenotype.

***Conclusion***: Non-cognitive features can be reliably measured by self-report in busy clinical settings. Such measurement can be useful in distinguishing patients with different etiologies of ND. Better characterization of unique, prodromal, non-cognitive ND trajectories could improve public health efforts to modify the course of ND for all patients at risk.

## 1. INTRODUCTION

Better description of non-cognitive syndromes that include medical, neurological and psychiatric symptoms could enable earlier identification of prodromal Neurodegenerative Disease (ND). The most common ND syndromes include Alzheimer's Disease (AD), Parkinson's Disease (PD), Dementia with Lewy Bodies (DLB), and Frontotemporal Lobar Degeneration (FTLD). For all ND's, pathophysiologic changes can be observed in the peripheral and central nervous system years before a patient meets clinical diagnostic criteria [1, 2]. Despite most ND being associated with cognitive changes, in fact the earliest symptoms of ND are non-cognitive. During prodromal phases of ND, specific symptoms in the domains of mood, motor, sleep and sensation become clinically detectable [3-6]. For example, in prodromal AD, non-cognitive changes including anxiety, irritability, and apathy and sleep inefficiency tend to predominate. In prodromal

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SN, non-cognitive symptoms including constipation, REM behavior and depression tend to predominate [7, 8]. Such features can be helpful in differential diagnosis, especially in the early stages [9]. Prodromal non-cognitive syndromes in AD relate to amyloidosis and other pre-tau pathological processes [10]. Prodromal syndromes in PD and DLB relate to the presence and location of Synucleinopathy (SN) [11].

Despite a growing understanding of the clinical phenomenology, epidemiology and pathology of ND in its later stages, the timing and significance of non-cognitive symptomatology in prodromal ND remains poorly understood. Cognitive and behavioral disorders are difficult to diagnose, especially at early stages. For people with Subjective Cognitive Impairment (SCI) or with mild cognitive symptoms below the threshold for a diagnosis of Mild Cognitive Impairment (MCI), clinicians lack pathologically-based clinical diagnostic criteria. Even at the Mild Cognitive Impairment (MCI) stage of AD, a significant number of cases are missed by trained clinicians [12]. Prodromal ND symptoms can be non-specific (Markopoulou *et al*., 2016). A host of factors including genetic, environmental, psychosocial, neurological, psychiatric and medical factors, modify neuropsychiatric function in adults [13]. Childhood developmental traits and late-life, age-related concomitant brain pathologies modify clinical presentations, creating diagnostic complexity. These are critical research gaps because disease-modifying interventions are most effective during prodromal stages.

The objective of this study was to describe medical, neurological and psychiatric symptomatology in patients clinically diagnosed with prodromal or early AD and/or PD/DLB. The hypothesis of this study was that non-cognitive symptoms would group together into different, recognizable symptom groups that are consistent with previously described, pathology-specific prodromal ND syndromes. This hypothesis is based on the epidemiological literature on prodromal ND [14-16].

A better understanding of the patterns of non-cognitive symptoms in prodromal ND could enable clinicians to more rapidly identify patients at risk. This is particularly important considering that interventions with risk reduction and disease modification are becoming in clinical and research settings. The global burden of ND due to AD, PD/LBD, and other dementias could be reduced through better identification of individuals harboring prodromal ND [17]. Accelerating efforts to identify preclinical stages of AD is therefore a key strategy of the U.S. National Plan to Address Alzheimer's Disease [18].

## 2. MATERIAL AND METHODS

This retrospective, observational study involved patients presenting to the Weill Cornell Medicine and New York-Presbyterian Memory Disorders Clinic between 2014 and 2017. The subject population included patients seen at the Alzheimer's Prevention Clinic who consented to the Comparative Effectiveness Dementia & Alzheimer's Registry (CEDAR). The CEDAR study is an observational study of clinical care delivered to patients seeking risk reduction and treatment services for dementia. Informed consent was obtained from all participants *via* a protocol approved by the institutional review board at Weill Cornell Medicine. Patients with incomplete data or prior dementia diagnoses were excluded.

As part of routine care, all subjects completed standardized assessments including neurological history, neurological examination, standardized cognitive testing, self-reported assessments, and diagnostic laboratory and imaging tests as indicated. The standardized assessment included National Institutes of Health Patient Reported Outcomes Measurement & Information System (NIH PROMIS) scales assessing depression, anxiety, alcohol use, and sleep [19], as well as other validated scales measuring sleep and perceived stress [20, 21]. Non-cognitive symptoms were identified through self-reported assessments using yes or no responses. These measures were chosen based on extensive literature review of the epidemiological risk factors and prodromal symptoms specific to different types of dementias [9, 16, 22-25]. Table **1** lists all of the measures used for evaluation.

**Table 1.   Clinical domains of assessment and measures.**

| Mood | Motor | Sleep | Autonomic/Sensory | |
|---|---|---|---|---|
| PROMIS Depression Scale Total Score | New problems with balance | Appearing to talk in sleep or act out your dreams | New problems with vision | Visual hallucinations |
| PROMIS Anxiety Scale Total Score | Tremor in hands or feet | PROMIS Sleep Disturbance Scale Score | Hearing Loss | New food cravings |
| PROMIS Alcohol Scale Total Score | Walking more slowly than before | Do you snore? | Unexplained episodes of dizziness or fainting | Loss of smell |
| PROMIS Social Isolation Scale Total Score | Decreased facial expressions | Trouble remembering dreams? | Chronic constipation | Change in appetite |
| Personality Changes | Shuffling of the feet | - | Chronic pain | Abnormal Sweating |
| Paranoia or delusions | Frequent falls | - | Trouble holding urine | Headaches |
| Agitation | Twitching | - | Dry skin or dandruff | Cold Intolerance |
| - | - | - | Numbness or tingling in the hands or feet | Impotence |

Cognition was measured using a battery of tests including the Mini-Mental State Exam, phonemic verbal fluency, categorical verbal fluency, Trail-Making Test, Boston Naming Test, as well as NIH Toolbox Cognition Battery (NIHTB-CB), Rey Auditory Verbal Learning Test (RAVLT), Auditory Verbal Learning, Dimensional Change Card Sort, Flanker Inhibitory Control and Attention, Pattern Comparison Process Speed, Odor Identification, Oral Symbol Digit, Picture Vocabulary, and Oral Reading Recognition [26-29]. The NIHTB-CB tests were chosen because of their validity for assessing cognitive function across a wide range of populations [30].

After the completion of each patients' initial visit, all relevant clinical information from each case was presented and interpreted at weekly team-based consensus conference where at least one neuropsychologist and one neurologist specializing in dementia were present. These conferences included a complete review of clinical history, neurological exam results, cognitive testing results, routine labs, and neuroimaging when available. Subjects were assigned to diagnostic groups using published diagnostic criteria [31-35]. Groups included: MCI due to AD, Detectable Cognitive Impairment (DCI) due to AD, MCI due to PD/LBD, DCI due to PD/LBD, MCI not otherwise specified (NOS), DCI NOS, Subjective Cognitive Impairment (SCI), and Normal Cognition (Table **2**).

DCI, a diagnostic category introduced in a prior manuscript [36], was assigned when patients could not be classified as having normal cognition and did not meet the threshold for MCI. While semantic in nature, DCI may be more accurately defined as a Detectible Cognitive Indicator, considering patients at this stage have no or minimal subjective complaints. Patients with DCI can be classified as DCI-AD, DCI-SN, or DCI-NOS by taking into account parkinsonian features from the neurological history and examination, AD-like cognitive findings (semantic, amnestic features), and the family history (Fig. **1**). DCI groups were subdivided in this study as shown in Table **2**. For simplicity of analysis, patients with mixed diagnostic categories, for example individuals classified as dual AD-DLB/PD, were excluded.

Laboratory-based biomarkers of neurodegenerative disease risk, including APOE4 and uric acid, were measured using standard clinical procedures. Patients were grouped as either APOE4 positive or negative. Uric acid was included in

**Table 2. Diagnostic grouping.**

| AD Pathology | Synucleinopathies | Other Neuro | Cognitively Normal |
|---|---|---|---|
| Amnestic MCI | Non Amnestic MCI - SN | Non Amnestic MCI - NOS | Normal |
| DCI-AD | DCI - SN | DCI - NOS | SCI |

MCI=mild cognitive impairment, SN=synucleinopathies, DCI=detectable cognitive impairment, SCI=Subjective cognitive impairment.
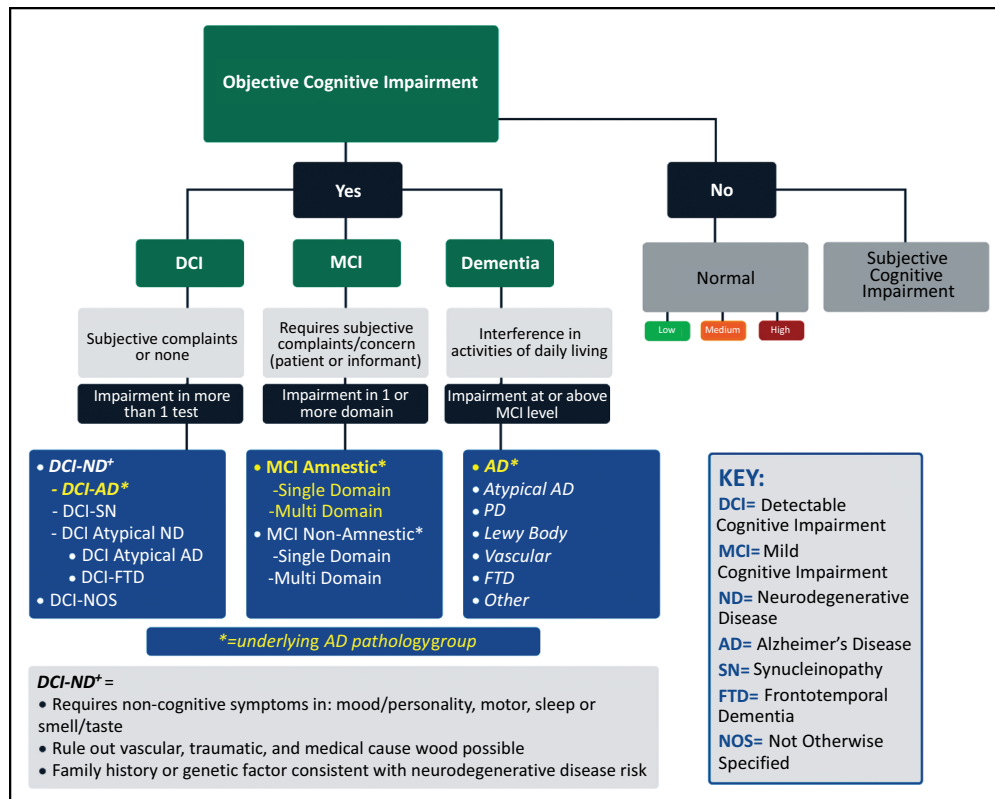


**Fig. (1).** Diagnostic groups classification system.

this analysis because it has been associated with the occurrence of PD-MCI in multiple studies [37]. Patients in the lowest quartile of uric acid were compared to patients in highest quartile of uric acid, since no established cutoff level currently exists [38].

In the primary analysis of this study, a Principal Component Analysis (PCA) was performed with data from the entire sample to identify the symptoms that clustered together. Factors were named according to the clinical syndrome each factor appeared to represent, if possible. Non-specific factors were assigned a generic name: "Other Factor 1", "Other Factor 2", *etc.* To test sampling adequacy for variables within the model the Kaiser-Meyer-Olkin (KMO) test was used and Bartlett's test of sphericty was used to test for interrelationships between variables prior to proceeding with Factor Analysis. To exclude a-priori assumptions regarding specific clinical diagnosis, (PCA) was performed on samples obtained from all diagnostic groups regardless of their clinical diagnoses. In sensitivity analyses, both symptom clusters and individual symptoms with significant contribution (factor loading > 0.7) were further analyzed using linear regression to identify a best-fitting regression model. The purpose of these steps was to test whether the clusters differed across diagnostic groups. In particular, subjects with any stage of AD (DCI-AD, MCI-AD, and AD) were compared to subjects with any stage of PD/LBD (DCI-PD, MCI-PD, and PD/LBD), Other Neuro, and Cognitively Normal.

## 3. RESULTS

A total of 165 patients were included in the study. Thirty-three patients were classified as having AD underlying pathology, 29 with synucleinopathy, 67 with Other ND, and 36 as Cognitively Normal. Table **3**. represents study sample demographics.

Using PCA, twelve factors emerged, which accounted for 63% of the total variance of the non-cognitive symptoms in the cohort (n = 165). Four syndrome-specific symptom factors emerged, and eight non-specific symptom factors.

The first factor group was named "Non-Motor phenotype" and consisted of personality changes, paranoia, hallucinations, cravings, agitation, and changes in appetite. The second factor group was named "Motor phenotype" and consisted of changes in appetite, walking, balance, hearing, increased falls, and dandruff [39]. The third factor group was named "AD-affective" and consisted of increased anxiety, depression, sleep disturbance, and social isolation, all measured using the PROMIS scales. The fourth factor group was named "Autonomic" and consisted of increased sweating, twitching, and tremor. The remaining factors and their symptom clusters are shown in Table **4**. The between group and within group differences are summarized in Table **5** and Fig. (**2**) outlines the predicted non-cognitive total score differences between diagnostic groups.

**Table 3.  Demographics.**

|  | AD Pathology (n=33) | Synucleinopathies (n=29) | Other Neuro (n=67) | Cognitively Normal (n=36) |
|---|---|---|---|---|
| **Age (years)** |  |  |  |  |
| Mean | 69.88 | 60.10 | 54.79 | 53.67 |
| Range | 43-93 | 33-74 | 31-89 | 28-86 |
| **Gender** |  |  |  |  |
| Males | 13 | 11 | 31 | 11 |
| Females | 20 | 18 | 36 | 25 |
| **Ethnicity** |  |  |  |  |
| White | 31 | 23 | 61 | 32 |
| Black | 1 | 2 | 2 | - |
| Native American | - | - | - | 1 |
| Asian Indian | - | - | 3 | 1 |
| Japanese | - | - | 1 | - |
| Other | - | 1 | 2 | 1 |
| Declined to Answer | 1 | 1 | - | 1 |
| **Education** |  |  |  |  |
| High School | 2 | 5 | 2 | 3 |
| Associates | 2 | 3 | - | 5 |
| Bachelors | 10 | 6 | 26 | 14 |
| Masters | 12 | 8 | 23 | 11 |
| Professional | 7 | 7 | 16 | 3 |

**Table 4.    PCA results.**

| | Rotated Component Matrix[a] | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Component | | | | | | | | | | | |
| - | Motor | Non-motor | AD | Essential Tremor | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| P value by Dx Group | 0.443 | .009* | 0.246 | 0.141 | .019* | .023* | 0.305 | 0.351 | 0.695 | 0.265 | 0.183 | 0.894 |
| ros_personality | 0.751 | - | - | - | - | - | - | - | - | - | - | - |
| ros_paranoia | 0.702 | - | - | - | - | - | - | - | - | - | - | - |
| ros_hallucinations | 0.699 | - | - | - | - | - | - | - | - | - | - | - |
| ros_cravings | 0.668 | - | - | - | - | - | - | - | - | - | - | - |
| ros_agitation | 0.544 | - | - | - | - | - | - | - | - | - | - | - |
| ros_appetite | 0.542 | - | - | - | - | - | - | - | - | - | - | - |
| ros_walking | - | 0.692 | - | - | - | - | - | - | - | - | - | - |
| ros_balance | - | 0.635 | - | - | - | - | - | - | - | - | - | - |
| ros_hearing | - | 0.585 | - | - | - | - | - | - | - | - | - | - |
| ros_falls | - | 0.555 | - | - | - | - | - | - | - | - | - | - |
| ros_dandruff | - | 0.491 | - | - | - | - | - | - | - | - | - | - |
| PROMIS Anxiety | - | - | 0.846 | - | - | - | - | - | - | - | - | - |
| PROMIS Depression | - | - | 0.820 | - | - | - | - | - | - | - | - | - |
| PROMIS Sleep Disturbance | - | - | 0.640 | - | - | - | - | 0.436 | - | - | - | - |
| PROMIS Social Isolation | - | - | 0.540 | - | - | - | - | - | - | - | - | - |
| ros_sweating | - | - | - | 0.744 | - | - | - | - | - | - | - | - |
| ros_twitch | - | - | - | 0.611 | - | - | - | - | - | - | - | - |
| ros_tremor | - | - | - | 0.525 | - | - | - | - | - | - | - | - |
| ros_headaches | - | - | - | - | 0.719 | - | - | - | - | - | - | - |
| ros_syncope | - | - | - | - | 0.704 | - | - | - | - | - | - | - |
| ros_shuffling | - | - | - | - | - | 0.766 | - | - | - | - | - | - |
| ros_impotence | - | - | - | - | - | 0.457 | - | - | - | - | - | - |
| ros_vision | - | - | - | - | - | - | 0.756 | - | - | - | - | - |
| ros_paresthesias | - | - | - | - | - | - | 0.597 | - | - | - | - | - |
| ros_incontinence | - | - | - | - | - | - | 0.508 | - | - | - | - | - |
| PROMIS Alcohol | - | - | - | - | - | - | - | 0.751 | - | - | - | - |
| ros_rem | - | - | - | - | - | - | - | 0.469 | - | - | - | - |
| ros_constipation | - | - | - | - | - | - | - | - | 0.773 | - | - | - |
| ros_face | - | - | - | - | - | 0.449 | - | - | 0.474 | - | - | - |
| ros_coldintolerance | - | - | - | - | - | - | - | - | - | 0.796 | - | - |
| ros_dreams | - | - | - | - | - | - | - | - | - | 0.557 | - | - |
| Do you snore? | - | - | - | - | - | - | - | - | - | - | 0.799 | - |
| ros_olfaction | - | - | - | - | - | - | - | - | - | - | -0.400 | - |
| ros_pain | - | - | - | - | - | - | - | - | - | - | - | 0.827 |

Extraction Method: Principal Component Analysis.  Rotation Method: Varimax with Kaiser Normalization[a].
a. Rotation converged in 20 iterations.

**Table 5.    ANOVA results.**

| - | | Sum of Squares | *df* | Mean Square | F | Sig. |
|---|---|---|---|---|---|---|
| **ros Cold Intolerance** | Between Groups | 0.740 | 3 | 0.247 | 1.506 | 0.218 |
| | Within Groups | 15.893 | 97 | 0.164 | - | - |
| | Total | 16.634 | 100 | - | - | - |
| **ros_olfaction** | Between Groups | 0.526 | 3 | 0.175 | 2.785 | 0.042 |
| | Within Groups | 10.642 | 169 | 0.063 | - | - |
| | Total | 11.168 | 172 | - | - | - |
| **Total Non-Cog** | Between Groups | 0.722 | 3 | 0.241 | 3.200 | **0.025** |
| | Within Groups | 12.943 | 172 | 0.075 | | - |
| | Total | 13.666 | 175 | | - | - |
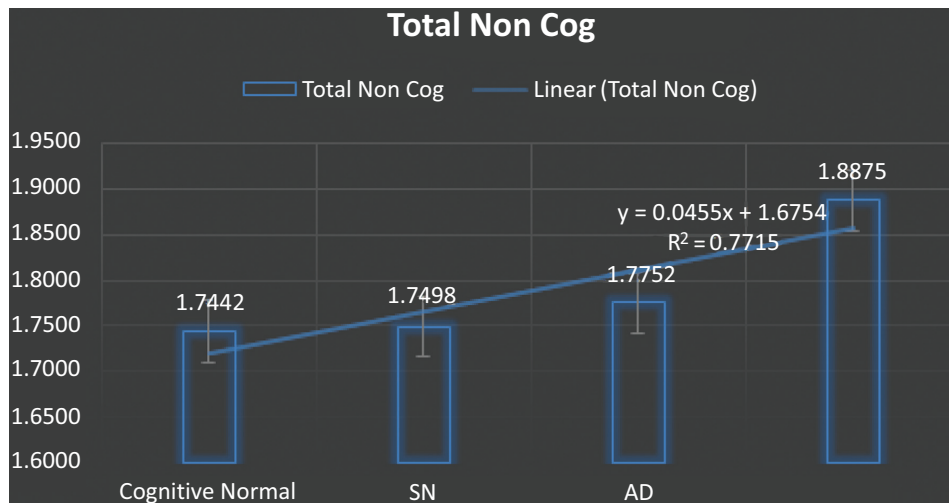


**Fig. (2).** Predicted non-cognitive total score differences between diagnostic groups.

## 4. DISCUSSION

In this study, medical, neurological and psychiatric symptoms in patients with different stages of early AD and PD/DLB were explored, analyzed and described. From clinical information derived from routine neurological history and evaluation, delivered to 165 patients with early stages of AD and PD and/or DLB, 4 specific syndromes and 8 non-specific factors (groups of symptoms) emerged. Specific factors included a Non-Motor Syndrome, a Motor Syndrome, an AD Affective Syndrome, and an Autonomic syndrome. These findings suggest that non-cognitive syndromes that could be indicative of prodromal ND can be reliably measured by self-report in busy clinical settings. The findings suggest that clinical approaches to detecting prodromal ND could be feasible. Non-motor symptoms (personality changes, paranoia, agitation, hallucinations, cravings, and changes in appetite) were more prominent in our PD/LBD group then our AD group. Interestingly, all factors were strongest in our PD/LBD diagnostic group.

One unexpected finding was that the presence of REM Behavioral symptomatology did not correlate strongly with any of the factors, even though REM behaviors have been reported to be strongly associated with PD/LBD [40]. This finding could be due to lack of a sensitive measurement for RBD and also RBD being a relatively later manifestation of synucleinopathy which is unlikely to occur a predominantly younger, minimally symptomatic population. Supporting this notion was the sensitivity analysis which showed that, when dementia patients were included in the analysis, the PCA included a new factor with REM behavior alongside other traditional symptoms of PD/LBD. Regarding sensitivity of detection, REM behaviors are difficult to detect and not noticed until they are more severe or have been present for a longer time period.

The findings of Motor, Neuropsychiatric, AD Affective and Autonomic syndrome factors are in line with several studies that compared non-cognitive symptoms to biomarker and imaging data. Babulal and colleagues found that AD biomarkers, including higher values of PET- Pittsburgh Compound B, Cerebral Spinal Fluid (CSF), total tauopathy, CSF phosphorylated tau, and lower CSF β-amyloid are associated with mood changes in cognitively normal older adults [10]. In addition, anxiety and depression among cognitively normal elderly adults has been linked to abnormalities in brain glucose metabolism, as measured by FDG-PET, in

regions associated with AD [3]. Further research has found that anxiety and irritability are associated with greater amyloid deposition in the neurodegenerative process leading to AD [41]. Lower levels of CSF β-amyloid has also been associated with decreased quality of sleep as measured as a percentage of time in bed spent asleep [5]. Direct evidence has linked non-motor symptoms, including hyposmia, constipation, depression, visual changes, small fiber neuropathy, and autonomic symptoms to PD, particularly in the pre-motor phase [11]. However, correlations with underlying pathology have been more difficult than in AD, given the lack of PD biomarkers. One study did demonstrate that deficits in dopamine transporters, measured by β-CIT SPECT imaging, were associated with hyposmia and constipation in patients' not meeting diagnostic criteria for PD [42].

This study adds to the prior literature by assessing a comprehensive set of symptoms, in a real-world clinical setting, in well-characterized patients at different stages of prodromal ND, including pre-MCI. Discerning which symptoms present together could give greater insight on the underlying pathology that is occurring during the development of NDs. Few studies have described differences in non-cognitive features between different diagnoses of ND.

Several limitations of this study are worth mentioning, as well as several strengths. Lack of pathological biomarkers for classifying each patient is a major limitation considering that the study is attempting to segregate non-cognitive features based on pathology. In addition, current diagnostic criteria have been written mostly with a research setting in mind. Although we used the conventional criteria, previous studies have shown high false positive (34.2%) and false negative (7.1%) rates [43, 44]. Validating the MCI and other diagnoses with CSF biomarkers or imaging data would improve accuracy. We attempted to address this limitation by conducting consensus conferences that included two dementia experts assessing each patient.

Another important limitation is the absence of criteria for classifying patients who are considered "not normal" but rather in between Normal and MCI. We addressed this limitation by developing a systematic algorithm for classifying these patients into a novel diagnostic category termed DCI [45], which may be most accurately referred to as Detectable Cognitive Indicator. DCI is characterized by cognitive deficits below the MCI threshold, in the presence of at least one non-cognitive symptom, as well as family history/genetic testing consistent with ND risk, without other explainable etiologies. Since non-cognitive features were included in the diagnosis of the patients, the possibility of reverse causation remains important. However, non-cognitive symptoms were not the only variable taken into account when classifying the DCI patients. In fact, the neurological examination and family history was more important for classifying patients with PD/LBD features.

## CONCLUSION

These findings may help clinicians begin to learn to recognize symptoms that may be part of prodromal ND syndromes. Greater physician awareness may ultimately lead to timely and accurate referrals for disease-modifying interventions to prevent ND. A thorough clinical history that takes into account prodromal, non-cognitive features could increase the accuracy of diagnoses made using biomarker testing which can be discordant in early stages of AD [46]. In addition, non-cognitive features might be useful in context where biomarker testing is less available. For patients in the prodromal stage of AD, biomarker testing such as CSF tests for amyloid and tau, or FDG-PET to assess for brain glucose hypometabolism, are not available through commercial insurance. Ultimately, earlier and more accurate diagnoses could lead to interventions that could modify disease if initiated in pre-MCI stages. Comprehensive lifestyle interventions, as well as anti-amyloid therapies appear to slow pathology in those at risk [47, 48]. Identifying the people who would benefit most from these interventions is a major national priority [18]. As such, additional work is indicated to develop clinical diagnostic criteria for pre-symptomatic stages. The possibility of applying such a framework in patients with other ND, such as frontotemporal dementia, and/or with multiple age-related and medical co-morbidities, is a major research priority.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Review Board at Weill Cornell Medicine, New York, USA.

## HUMAN AND ANIMAL RIGHTS

No animals were used in this study, the reported experiments on humans were in accordance with the ethical standards of the committee responsible for human experimentation (institutional national), and with the Helsinki Declaration of 1975, as revised in 2008 (http://www.wma.net/).

## CONSENT FOR PUBLICATION

Informed consent was obtained from all participants.

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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