

**N-ACETYL-LEUCINE FOR USE IN THE TREATMENT OF PRODROMAL
ALPHA-SYNUCLEINOPATHIES**

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application Nos. 63/620,240, filed January 12, 2024; 63/554,373, filed February 16, 2024; and 63/692,804, filed September 10, 2024. The contents of each of these applications are incorporated herein by reference in their entirety.

BACKGROUND

[0002] Parkinson's disease (PD) is characterized by the progressive loss of neural function and death of neurons that use the neurotransmitter dopamine. Late symptoms of fully manifested PD involve motor (movement) dysfunction, resulting in tremors and rigidity. Prodromal symptoms manifest earlier, sometimes up to 15 years, before converting to manifest PD. Prodromal PD refers to the stage at which individuals do not fulfill diagnostic criteria for "manifest PD" or "classical PD," i.e., bradykinesia and at least one other motor sign, but exhibit signs and symptoms that indicate a higher than average risk of developing motor symptoms and a diagnosis of PD in the future. The best-characterized symptoms of prodromal PD include alterations in autonomic function (constipation), loss of smell (hyposmia), changes in glucose metabolism, and REM-sleep behavior disorder (RBD) in which dreams are violently acted out and may, for example, result in the unintentional physical assault of their sleeping partner. These prodromal symptoms serve as an accurate and predictive early-stage biomarker for Parkinson's disease, as patients with these symptoms have a >85 % risk of conversion to PD or dementia with Lewy bodies (DLB), within 10-15 years (Postuma et al., 2019; Janzen et al., 2022). There exists a need for therapeutic agents to treat the prodromal phase of PD and other alpha-synucleinopathies.

BRIEF SUMMARY

[0003] In one aspect, the present disclosure provides methods of treating the prodromal phase of an alpha-synucleinopathy, e.g., Parkinson's disease (PD), dementia with Lewy bodies (DLB), or multiple systems atrophy (MSA), in a subject in need thereof, the

method comprising administering a therapeutically effective amount of N-acetyl-leucine to the subject.

[0004] In another aspect, the subject (i) is not diagnosed with any of the core clinical features, syndromes, or symptoms associated with the alpha-synucleinopathy; and (ii) is diagnosed with one or more core clinical features, syndromes, or symptoms associated with the prodromal phase of the alpha-synucleinopathy.

[0005] In another aspect, the present disclosure provides methods of treating the prodromal phase of PD, wherein the subject (i) is not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and (ii) is diagnosed with one or more of hyposmia, cognitive impairment, REM-sleep behavior disorder (RBD), constipation, depression, and/or anxiety.

In another aspect, the present disclosure provides methods of treating the prodromal phase of DLB, wherein the subject (i) is not diagnosed with dementia; and (ii) is diagnosed with one or more of RBD, constipation, hyposmia, depression, and/or orthostatic hypotension/dizziness.

[0006] In another aspect, the present disclosure provides methods of treating the prodromal phase of MSA, wherein the subject (i) is not diagnosed with (a) an autonomic dysfunction; and (b) poorly L-dopa-responsive parkinsonism and/or cerebellar syndrome; and (ii) is diagnosed with one or more of RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and/or urogenital failure.

[0007] In another aspect, the present disclosure provides methods of treating RBD in a subject in need thereof, the method comprising administering a therapeutically effective amount of N-acetyl-leucine to the subject.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

[0008] FIGs. 1A-1B depict the subjective severity score of the REM-Sleep-Behavior Disorder phenotype of Patient 1 (FIG. 1A) and Patient 2 (FIG. 1B) after treatment with N-acetyl-DL-leucine. 21 daily scores were summed up to a 3 week sumscore (RBD-SS-3). The total observation period was three weeks and RBD-SS-3 values of the first 18 weeks are shown in the first half of FIGs. 1A-1B and RBD-SS-3 values of the last 18 weeks are shown in the second half of FIGs. 1A-1B.

[0009] FIGs. 2A-2B depict the DAT-SPECT results of Patient 1 (FIG. 2A) and Patient 2 (FIG. 2B) prior to and after administration of N-acetyl-DL-leucine. The upper panel shows representative images of DAT-SPECT in the striatum. The lower panel depicts striato-occipital ratio in the left striatum (Striatum-L), right striatum (Striatum-R), left caudate nucleus (Caudate-L), right caudate nucleus (Caudate-R), left putamen (Putamen-L) and the right putamen (Putamen-R). The DAT-ligand-binding ratio (in the Putamen-R) is shown below the image in the upper panel.

[0010] FIGs. 3A-3B depict the FDG-PET results of Patient 1 (FIG. 3A) and Patient 2 (FIG. 3B) prior to and after administration of N-acetyl-DL-leucine.

DETAILED DESCRIPTION

I. Definitions

[0011] A "subject", as used herein, may be a vertebrate, mammal or domestic animal. Hence, compositions according to the disclosure may be used to treat any mammal, for example livestock (e.g. a horse, cow, sheep or pig), pets (e.g. a cat, dog, rabbit or guinea pig), a laboratory animal (e.g. a mouse or rat), or may be used in other veterinary applications. In one embodiment, the subject is a human being.

[0012] As used herein, the singular forms "a," "an," and "the" include plural reference.

[0013] The terms "approximately" and "about" mean to be nearly the same as a referenced number or value including an acceptable degree of error for the quantity measured given the nature or precision of the measurements. As used herein, the terms "approximately" and "about" should be generally understood to encompass $\pm 10\%$ of a specified amount, frequency or value. Numerical quantities given herein are approximate unless stated otherwise, meaning that term "about" or "approximately" can be inferred when not expressly stated.

[0014] The terms "administer," "administration," or "administering" as used herein refer to (1) providing, giving, dosing and/or prescribing by either a health practitioner or his authorized agent or under his direction a composition according to the disclosure, and (2) putting into, taking or consuming by the patient or person himself or herself, a composition according to the disclosure.

- [0015] References to "N-acetyl-leucine" throughout include pharmaceutically acceptable salts of the same, even if not expressly stated. The acetyl-leucine may be in racemic form, which means that the compound comprises about equal amounts of enantiomers. Alternatively it may be present in an enantiomeric excess of either the L-enantiomer or the D-enantiomer. The N-acetyl-leucine may be in a single enantiomeric form of either the L-enantiomer or the D-enantiomer. In one embodiment, the single enantiomeric form is the L-enantiomer. The racemic and enantiomeric forms of N-acetyl-leucine may be obtained in accordance with known procedures in the art.
- [0016] A "pharmaceutically acceptable carrier" as referred to herein, is any known compound or combination of known compounds that are known to those skilled in the art to be useful in formulating pharmaceutical compositions. It will be appreciated that the carrier of the pharmaceutical composition should be one which is tolerated by the subject to whom it is given.
- [0017] A "pharmaceutically acceptable salt" as referred to herein, is any salt preparation that is appropriate for use in a pharmaceutical application. Pharmaceutically acceptable salts include, but are not limited to, amine salts, such as N,N'-dibenzylethylenediamine, chlorprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, l-para-chloro-benzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines, piperazine, tris(hydroxymethyl)aminomethane and the like; alkali metal salts, such as lithium, potassium, sodium and the like; alkali earth metal salts, such as barium, calcium, magnesium and the like; transition metal salts, such as zinc, aluminum and the like; other metal salts, such as sodium hydrogen phosphate, disodium phosphate and the like; mineral acids, such as hydrochlorides, sulfates and the like; and salts of organic acids, such as acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates, fumarates and the like.
- [0018] A "therapeutically effective amount" of an agent is any amount which, when administered to a subject, is the amount of agent that is needed to produce the desired effect, which, for the present disclosure, can be therapeutic and/or prophylactic. The dose may be determined according to various parameters, such as the specific form of N-acetyl-leucine used; the age, weight and condition of the patient to be treated; the type of the disease; the route of administration; and the required regimen. A physician will be

able to determine the required route of administration and dosage for any particular patient.

[0019] The terms "symptom," "syndrome," or "core clinical feature" refers to any clinical or laboratory manifestation associated a disease, disorder, or illness and is not limited to what the subject can feel or observe. Symptoms as described herein include, but are not limited to, neurological symptoms and psychiatric symptoms.

[0020] The terms "synucleinopathy," "a-synucleinopathy," or "alpha-synucleinopathy" refers to neurodegenerative diseases characterized by the abnormal accumulation of aggregates of alpha-synuclein protein in neurons, nerve fibres, or glial cells. There are three main types of synucleinopathy: Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Other rare disorders, such as various neuroaxonal dystrophies, also have alpha-synuclein pathologies.

[0021] The terms "prodromal" or "prodromal phase" refers to the time period between the appearance of initial signs or symptoms and the development of the full disease, illness, or condition.

[0022] A "subject in need thereof" as used herein may be any subject who has a disease, disorder, condition, or syndrome characterized by abnormal accumulation of alpha-synuclein. The subject may or may not have been diagnosed with the disease, disorder, condition, or syndrome. For example, the subject may not yet have a diagnosis (clinical or otherwise) of an alpha-synucleinopathy, but may have one or more symptoms of an alpha-synucleinopathy.

[0023] The term "and/or" as used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term "and/or" as used in a phrase such as "A and/or B" herein is intended to include "A and B," "A or B," "A" (alone), and "B" (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0024] The phrase "subject is not diagnosed" and the like as used herein means that the relevant clinical feature, syndrome, or symptom of a disease, e.g., the prodromal phase of an alpha-synucleinopathy or the classical alpha-synucleinopathy, has not been identified in the subject through examination by a physician or other qualified health care provider.

II. Alpha-synucleinopathies

- [0025] Alpha-synucleinopathies are neurodegenerative disorders characterized by abnormal accumulation of aggregates of alpha-synuclein protein in neurons, nerve fibers, or glial cells. The three main types of alpha-synucleinopathies include Parkinson's disease (PD), dementia with Lewy bodies (DLB), or multiple systems atrophy (MSA).
- [0026] In some embodiments, the disclosure provides methods of treating the prodromal phase of an alpha-synucleinopathy in a subject in need thereof, the method comprising administering a therapeutically effective amount of N-acetyl-leucine to the subject.
- [0027] In some embodiments, the subject is not diagnosed with any of the core clinical features, syndromes, or symptoms associated with the alpha-synucleinopathy.
- [0028] In some embodiments, the subject is diagnosed with one or more core clinical features, syndromes, or symptoms associated with the prodromal phase of the alpha-synucleinopathy.
- [0029] In some embodiments, the subject is: (i) not diagnosed with any of the core clinical features, syndromes, or symptoms associated with the alpha-synucleinopathy; and (ii) is diagnosed with one or more core clinical features, syndromes, or symptoms associated with the prodromal phase of the alpha-synucleinopathy.
- [0030] In some embodiments, the alpha-synucleinopathy is Parkinson's disease (PD), dementia with Lewy bodies (DLB), or multiple systems atrophy (MSA).

A. Parkinson's disease

- [0031] In some embodiments, the disclosure provides methods of treating the prodromal phase of Parkinson's disease in a subject in need thereof comprising administering a therapeutically effective amount of N-acetyl-leucine to the subject. These subjects are referred to in this section as a "prodromal Parkinson's disease subject" or "PPD subject."
- [0032] In some embodiments, the PPD subject is not diagnosed with any of the core clinical features, syndromes, or symptoms associated with Parkinson's disease. In some embodiments, the core clinical features, syndromes, or symptoms associated with Parkinson's disease are tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination.
- [0033] In some embodiments, the PPD subject is not diagnosed with any one of tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination.

- [0034] In some embodiments, the PPD subject is not diagnosed with any two of tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination.
- [0035] In some embodiments, the PPD subject is not diagnosed with any three of tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination.
- [0036] In some embodiments, the PPD subject is not diagnosed with any four of tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination.
- [0037] In some embodiments, the PPD subject is not diagnosed with any of tremor, bradykinesia, muscle stiffness, impaired balance, and impaired coordination.
- [0038] In some embodiments, the PPD subject is diagnosed with one or more core clinical features, syndromes, or symptoms associated with the prodromal phase of PD. In some embodiments, the core clinical features, syndromes, or symptoms associated with the prodromal phase of PD are hyposmia, cognitive impairment, REM-sleep behavior disorder (RBD), constipation, depression, and/or anxiety.
- [0039] In some embodiments, the PPD subject is diagnosed with one of hyposmia, cognitive impairment, RBD, constipation, depression, and/or anxiety.
- [0040] In some embodiments, the PPD subject is diagnosed with two of hyposmia, cognitive impairment, RBD, constipation, depression, and/or anxiety.
- [0041] In some embodiments, the PPD subject is diagnosed with three of hyposmia, cognitive impairment, RBD, constipation, depression, and/or anxiety.
- [0042] In some embodiments, the PPD subject is diagnosed with four of hyposmia, cognitive impairment, RBD, constipation, depression, and/or anxiety.
- [0043] In some embodiments, the PPD subject is diagnosed with five of hyposmia, cognitive impairment, RBD, constipation, depression, and/or anxiety.
- [0044] In some embodiments, the PPD subject is diagnosed with hyposmia, cognitive impairment, RBD, constipation, depression, and anxiety.
- [0045] In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and (ii) is diagnosed with one or more of hyposmia, cognitive impairment, RBD, constipation, depression, and/or anxiety.
- [0046] Parkinson's disease (PD) is characterized by certain clinical features, such as bradykinesia, rigidity, and resting tremor, and is associated with progressive neuronal loss in substantia nigra and other brain regions. A clear response to dopaminergic therapy and

the presence of either olfactory loss or cardiac sympathetic denervation are supportive criteria. Moreover, diagnosis of clinically established PD requires absence of the features of atypical parkinsonian syndromes (APSs). Atypical parkinsonian syndromes include multiple systems atrophy (MSA), progressive supranuclear palsy, and corticobasal degeneration. (Zhao et al., *Brain and Behavior*, 1-9 (2020)).

[0047] Among the three cardinal symptoms of PD, bradykinesia is the most important and mainly contributes to the disability associated with PD progression. The term bradykinesia refers to the slowness and poverty of voluntary and involuntary movements characteristic of parkinsonism. Muscular rigidity, defined as the increased resistance of a joint to passive movements, only minimally contributes to the impairment experienced by parkinsonian patients. The subjective correlate of rigidity is a feeling of stiffness and reduced ability to relax limb and trunk muscles. Tremor is the most conspicuous of the cardinal symptoms of PD, and gave rise to the initial name of the disease, shaking palsy, by James Parkinson in 1817. Parkinsonian tremor usually occurs during rest, and typically affects the upper limbs, but may also occur in the legs and less frequently in the head. Although resting tremor is not necessarily disabling, many patients suffer considerably from it, not least because tremor stigmatizes them as parkinsonian subjects. (Pellicano et al., *Neuropsychiatric Disease and Treatment*, 3(1), 145-151 (2007)).

[0048] Recent neuropathological data indicate that the pathological landmark of PD, the Lewy bodies, can be identified in several neuronal populations other than the dopaminergic mesencephalic ones. Following the ascending gradient of neuronal involvement throughout disease progression, six neuropathological stages of PD have been identified (Braak staging): in stages 1 and 2, defined as “presymptomatic stages,” the Lewy bodies are confined to the anterior olfactory nucleus, olfactory bulb, dorsal motor nucleus of the glossopharyngeal and vagal nerves, locus coeruleus, and reticular formation. In stages 3 and 4 (“intermediate stages”), the neuropathological damage extends to the substantia nigra pars compacta, other mesencephalic nuclei, the prosencephalon and meso-allocortical regions; during these stages, the motor symptoms develop and progressively worsen. Eventually, in stages 5 and 6 (“advanced stage” of PD), neocortical, prefrontal, and associative cortices are pathologically involved; in these latter stages, severe motor disturbances are accompanied by cognitive and behavioral

symptoms. (Pellicano et al., Neuropsychiatric Disease and Treatment, 3(1), 145-151 (2007); Mahlkecht et al., J Parkinson's Disease, 5, 681-697 (2015)).

Table 1

The Phases of Parkinson's Disease
(Mahlkecht et al., J Parkinson's Disease, 5, 681-697 (2015))

Phase of PD	Clinical Status	Pathology
Phase 1 – preclinical	No clinical signs or symptoms	PD-specific pathology assumed to be present
Phase 2 – prodromal	Early nonmotor symptoms ± early subtle motor symptoms	Extranigral PD pathology (Braak stages 1 and 2) ± nigral PD pathology (<40-60% cell loss; Braak stage 3)
Phase 3 - motor	Classical motor manifestations are present	Nigral PD pathology (>40-60% cell loss; Braak stages 3 to 6)

[0049] The prodromal phase of PD is characterized by a range of non-motor symptoms that can predate the onset of the motor symptoms for many years. (Roos et al., J Parkinson's Disease, 12, 967-974 (2022)). These symptoms include constipation, hyposmia (olfactory loss), RBD, depression, anxiety disorder, and cognitive impairment. (Hustad et al., Front. Neurol., 11:395 (2020)).

[0050] The symptoms of prodromal PD include sensory symptoms, neuropsychiatric symptoms, behavioral symptoms, autonomic dysfunction, and sleep disorders. The sensory symptoms of prodromal PD include hyposmia, visual abnormalities, e.g., reduced color vision, and pain. The neuropsychiatric symptoms of prodromal PD include depression, anxiety, anhedonia, apathy, and frontal executive dysfunction. The behavioral symptoms of prodromal PD include quitting smoking. The autonomic dysfunction symptoms of prodromal PD include constipation, orthostatic hypotension, and urogenital dysfunction. The sleep disorder symptoms of prodromal PD include RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during

sleep (PLMS), and restless leg syndrome (RLS). (Mahlknecht et al., J Parkinson's Disease, 5, 681-697 (2015)) The non-motor symptoms of prodromal Parkinson's Disease are shown in Table 2.

Table 2

Non-motor Symptoms of Prodromal Parkinson's Disease (Mahlknecht et al., J Parkinson's Disease, 5, 681-697 (2015))

Nonmotor symptom	May occur prior to motor symptoms	Timespan before motor onset	Sensitivity for future PD	Specificity for future PD
<i>Sensory symptoms</i>				
Hyposmia	++	Medium (up to 5-10 years)	High (>80% PD patients affected)	Low (>30% of elderly have hyposmia)
Visual abnormalities (e.g., reduced colour vision)	+	Unknown (in RBD up to 10 years)	Unknown	Unknown
Pain	+/-			
<i>Neuropsychiatric symptoms</i>				
Depression and anxiety	++	Medium (up to 10 years)	Low (30-40% of PD patients affected)	Low (common in the elderly population)
Anhedonia and apathy	+/-			
Frontal executive dysfunction	+/-			
<i>Behavioural symptoms</i>				
Quitting smoking	+	Long (mean 10 years)	Unknown	Unknown
<i>Autonomic dysfunction</i>				
Constipation	++	Long (potentially more than 10-20 years)	Moderate (30-60% of PD patients affected)	Low (common in the elderly population)
Orthostatic hypotension	+/-			
Urogenital dysfunction	+/-			
<i>Sleep disorders</i>				

RBD	++	Long (potentially more than 10-20 years)	Low to moderate (30-50% of PD patients affected)	High (<80% of idiopathic RBD patients will develop Lewy- body disorders)
Excessive daytime somnolence	+	Medium (5-10 years)	Unknown	Unknown
Sleep fragmentation and insomnia	+/-			
PLMS/RLS	+/-			

PD, Parkinson's disease; PLMS, periodic limb movements during sleep; RBD, rapid eye movement sleep behavior disorder; RLS, restless legs syndrome. ++ = robust evidence from more than one prospective population-based or cohort study, + = evidence from one prospective population-based or cohort study or more than one retrospective population-based or cohort study, +/- = no evidence from population based or cohort studies, but respective nonmotor symptom is frequently seen in early PD

[0051] Some of the symptoms associated with prodromal PD are not specific to PD and can also be caused by other diseases. It is therefore unlikely that prodromal PD can be diagnosed based on one single prodromal marker. Instead, the coincidence of multiple markers (risk factors) in a single individual may be a more reliable indicator of prodromal PD. The Honolulu-Asia Aging Study (HAAS) examined olfaction, constipation, executive functioning, and excessive daytime sleepiness in elderly subjects (mean age 79.7 years), and revealed that persons with two or more risk factors had a 10-fold increase in the risk of developing PD. The Prospective evaluation of Risk factors for Idiopathic Parkinson's Syndrome (PRISP) study, including participants with a mean age of 59 years, found that the combination of prescreening for age, a positive family history and/or hyposmia and secondary screening for enlarged substantia nigra hyperechogenicity predicted PD. In the Parkinson At-Risk Syndrome (PARS) study the number of other non-motor symptoms (anxiety, RBD and constipation) was higher in hyposmic subjects than in normosmic subjects, who were approximately 64 years old. (Roos et al., J Parkinson's Disease, 12, 967-974 (2022)).

- [0052] In some embodiments, the PPD subject is diagnosed with one or more core clinical features, syndromes, or symptoms associated with the prodromal phase of Parkinson's disease. In some embodiments, the core clinical features, syndromes, or symptoms associated with the prodromal phase of Parkinson's disease are hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).
- [0053] In some embodiments, the PPD subject is diagnosed with one or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).
- [0054] In some embodiments, the PPD subject is diagnosed with two or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).
- [0055] In some embodiments, the PPD subject is diagnosed with three or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).
- [0056] In some embodiments, the PPD subject is diagnosed with four or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

- [0057] In some embodiments, the PPD subject is diagnosed with five or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).
- [0058] In some embodiments, the PPD subject is diagnosed with six or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).
- [0059] In some embodiments, the PPD subject is diagnosed with seven or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).
- [0060] In some embodiments, the PPD subject is diagnosed with eight or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).
- [0061] In some embodiments, the PPD subject is diagnosed with nine or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).
- [0062] In some embodiments, the PPD subject is diagnosed with ten or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety,

anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0063] In some embodiments, the PPD subject is diagnosed eleven one or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0064] In some embodiments, the PPD subject is diagnosed with twelve or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0065] In some embodiments, the PPD subject is diagnosed with thirteen or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0066] In some embodiments, the PPD subject is diagnosed with fourteen or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0067] In some embodiments, the PPD subject is diagnosed with fifteen or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation,

insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0068] In some embodiments, the PPD subject is diagnosed with sixteen or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0069] In some embodiments, the PPD subject is diagnosed with hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and restless leg syndrome (RLS).

[0070] In some embodiments, the core clinical features, syndromes, or symptoms associated with the prodromal phase of Parkinson's disease are hyposmia, cognitive impairment, RBD, constipation, depression, and anxiety. In some embodiments, the PPD subject is diagnosed with one or more of hyposmia, cognitive impairment, RBD, constipation, depression, and/or anxiety.

[0071] In some embodiments, the PPD subject is diagnosed with two or more of hyposmia, cognitive impairment, RBD, constipation, depression, and/or anxiety. In some embodiments, the PPD subject is diagnosed with three or more of hyposmia, cognitive impairment, RBD, constipation, depression, and/or anxiety. In some embodiments, the PPD subject is diagnosed with four or more of hyposmia, cognitive impairment, RBD, constipation, depression, and/or anxiety. In some embodiments, the PPD subject is diagnosed with five or more of hyposmia, cognitive impairment, RBD, constipation, depression, and/or anxiety. In some embodiments, the PPD subject is diagnosed with hyposmia, cognitive impairment, RBD, constipation, depression, and anxiety.

[0072] In some embodiments, the PPD subject is diagnosed with one or more of hyposmia, RBD, and/or constipation. In some embodiments, the PPD subject is diagnosed with two or more of hyposmia, RBD, and/or constipation. In some embodiments, the PPD subject is diagnosed with hyposmia, RBD, and constipation. In some embodiments, the PPD subject is (i) not diagnosed with any of the core clinical features, syndromes, or

symptoms associated with Parkinson's disease; and the PPD subject is (ii) diagnosed with one or more core clinical features, syndromes, or symptoms associated with the prodromal phase of Parkinson's disease.

[0073] In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with one or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0074] In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with two or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0075] In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with three or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0076] In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with four or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0077] In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with five or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0078] In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with six or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0079] In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with seven or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0080] In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with eight or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0081] In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with nine or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive

dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0082] In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with ten or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0083] In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with eleven or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0084] In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with twelve or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0085] In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with thirteen or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

- [0086] In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with fourteen or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).
- [0087] In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with fifteen or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).
- [0088] In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with sixteen or more of hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).
- [0089] In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, RBD, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and restless leg syndrome (RLS).
- [0090] In some embodiments, the PPD subject is: (i) not diagnosed with any of the core clinical features, syndromes, or symptoms associated with Parkinson's disease and the PPD subject is (ii) diagnosed with one or more core clinical features, syndromes, or symptoms associated with the prodromal phase of Parkinson's disease.

- [0091] In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with one or more of hyposmia, cognitive impairment, RBD, constipation, depression, and/or anxiety.
- [0092] In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with two or more of hyposmia, cognitive impairment, RBD, constipation, depression, and/or anxiety.
- [0093] In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with three or more of hyposmia, cognitive impairment, RBD, constipation, depression, and/or anxiety.
- [0094] In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with four or more of hyposmia, cognitive impairment, RBD, constipation, depression, and/or anxiety.
- [0095] In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with five or more of hyposmia, cognitive impairment, RBD, constipation, depression, and/or anxiety.
- [0096] In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with hyposmia, cognitive impairment, RBD, constipation, depression, and anxiety.
- [0097] In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with one or more of hyposmia, RBD, and constipation. In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with two or more of hyposmia, RBD, and constipation. In some embodiments, the PPD subject is: (i) not diagnosed with tremor, bradykinesia, muscle

stiffness, impaired balance, and/or impaired coordination; and the PPD subject is (ii) diagnosed with hyposmia, RBD, and constipation.

[0098] Almost all PD patients suffer from constipation. Constipation is characterized by infrequent stools, difficult stool passage, or both, is one of the first, most common and disabling non-motor symptoms to develop during the prodromal phase. Constipation is among the first prodromal signs, occurring up to 20 years prior to the first motor symptoms. (Pellicano et al., *Neuropsychiatric Disease and Treatment*, 3(1), 145-151 (2007)).

[0099] In some embodiments, the PPD subject is diagnosed with constipation. In some embodiments, administration of N-acetyl-leucine reduces the frequency of constipation in the PPD subject compared to prior to administration of N-acetyl-leucine. In some embodiments, administration of N-acetyl-leucine decreases the frequency of constipation in the PPD subject compared to prior to administration of N-acetyl-leucine. In some embodiments, administration of N-acetyl-leucine reduces the severity of constipation in the PPD subject compared to prior to administration of N-acetyl-leucine.

[0100] Hyposmia (decreased sense of smell) is one of the most common and best-characterized non-motor features of PD and is often one of the earliest prodromal features to emerge. More than 50% of patients suffering PD experience anosmia (loss of the sense of smell), 35% of patients have severe hyposmia and 14% of patients moderate hyposmia. (Pellicano et al., *Neuropsychiatric Disease and Treatment*, 3(1), 145-151 (2007)). Hyposmia can be objectively quantified with standard tests such as sense of smell tests including a 12-item Brief Smell Identification Test (B-SIT) and/or sniffin sticks test (SST) evaluating three different aspects of olfactory function (threshold (T), discrimination (D) and identified (I)), nasal endoscopy, and/or imaging tests including computer tomograph (CT) and magnetic resonance imaging (MRI). In some embodiments, the PPD subject is diagnosed with hyposmia. In some embodiments, the PPD subject is diagnosed with hyposmia using a 12-item Brief Smell Identification Test (B-SIT). In some embodiments, the PPD subject is diagnosed with hyposmia using sniffin sticks test (SST).

[0101] In some embodiments, the PPD subject is diagnosed with hyposmia. In some embodiments, administration of N-acetyl-leucine reduces the severity of hyposmia in the PPD subject compared to prior to administration of N-acetyl-leucine

[0102] Virtually all PD patients develop sleep disruption, and there is evidence that the process usually begins early in the course of the disease. RBD is a parasomnia characterized by dream-enacting behavior typically involving vocalizations or movements of the upper extremities, related to unpleasant dreams and loss of normal REM-sleep muscle atonia. Patient-reported questionnaires have been developed for identification of individuals with RBD, but similarly to patients with hyposmia, patients with RBD are often not aware of their symptoms. Accurate collateral history from a bed partner is usually necessary to make the diagnosis. In questionable cases or for individuals without bed partners, polysomnography can be obtained. Cohort studies indicate that iRBD convert to PD and other synucleinopathies such as dementia with Lewy bodies and multiple systems atrophy. In some embodiments, the PPD subject is diagnosed with RBD. In addition to RBD, recent data suggest that excessive daytime sleepiness may also be a pre-motor marker of PD (Pellicano et al., *Neuropsychiatric Disease and Treatment*, 3(1), 145-151 (2007)).

[0103] In some embodiments, the PPD subject is diagnosed with a sleep disorder. In some embodiments, the sleep disorder is RBD. RBD may be isolated (iRBD) when non-associated to other neurological diseases. In some embodiments, the PDD subject is diagnosed with iRBD. RBD and iRBD may be used interchangeably herein.

[0104] In some embodiments, administration of the N-acetyl-leucine reduces the number of RBD episodes as compared to the number of RBD episodes prior to administration of the N-acetyl-leucine. In some embodiments, administration of the N-acetyl-leucine reduces the PPD subject's RBD daily severity score as compared to the PPD subject's RBD daily severity score prior to administration of the N-acetyl-leucine.

[0105] In some embodiments, administration of the N-acetyl-leucine reduces the frequency of RBD behaviors compared to prior to administration of the N-acetyl-leucine. In some embodiments, the RBD behaviors are selected from the group consisting of vocalizations, simple and complex motor behaviors, and any combination thereof. In some embodiments, administration of the N-acetyl-leucine reduces the severity of RBD behaviors compared to prior to administration of the N-acetyl-leucine.

[0106] In some embodiments, administration of the N-acetyl-leucine decreases the number of nights with injurious behaviors to the PPD subject or bed partner per week compared to prior to administration of the N-acetyl-leucine. In some embodiments, the

injurious behaviors are selected from a group consisting of vocalizations, simple and complex motor behaviors, and any combination thereof.

[0107] In some embodiments, administration of the N-acetyl-leucine decreases the number of nightmares per week compared to prior to administration of the N-acetyl-leucine.

[0108] Depression is extremely frequent in PD, occurring in up to 45% of cases. Depression is not necessarily related to the severity of motor symptoms of PD, and is often misdiagnosed since hypomimia and reduction of voluntary movements are common to both PD and pure depression. Therefore, the identification of depression in PD patients is essentially based upon subjective perception of depressive symptoms such as feeling of incapability, reduced reaction to emotional stimuli, and inability to experience pleasure from things and events (anhedonia). The pathophysiology of depression in PD is rather complex, being related to damage of the noradrenergic, serotonergic and dopaminergic pathways in the brain. Indeed, the pattern of depressive symptoms in PD appears different from that of pure depression. Typical signs of depression in PD are a raised degree of dysphoria and irritability, pessimism about future, with low levels of inadequacy and sense of guilt. (Pellicano et al., *Neuropsychiatric Disease and Treatment*, 3(1), 145-151 (2007)).

[0109] In a case-control study, the occurrence of depression in the last 5 years was significantly linked to future development of motor symptoms of PD. A longitudinal study showed the increased risk of developing PD in depressed subjects as compared to not depressed ones. Finally, Lauterbach et al (2004) reported that patients with PD more often had a primary (preceding the onset of PD) diagnosis of single phobia and a secondary atypical depression than did those with dystonia. (Pellicano et al., *Neuropsychiatric Disease and Treatment*, 3(1), 145-151 (2007)).

[0110] In some embodiments, the PPD subject is diagnosed with depression. In some embodiments, administration of the N-acetyl-leucine decreases the severity of depression compared to prior to administration of the N-acetyl-leucine. In some embodiments, administration of the N-acetyl-leucine reduces the number of depressive episodes in the PPD subject compared to prior to administration of the N-acetyl-leucine.

[0111] Anxiety is also common in PD, and may represent a premotor risk factor. Anxiety can be present as panic attacks, phobias, or generalized anxiety disorder, and can be

related to drug-induced motor fluctuations in PD. (Pellicano et al., *Neuropsychiatric Disease and Treatment*, 3(1), 145-151 (2007)).

- [0112] In some embodiments, the PPD subject is diagnosed with anxiety. In some embodiments, administration of the N-acetyl-leucine decreases the severity of anxiety compared to prior to administration of the N-acetyl-leucine. In some embodiments, administration of the N-acetyl-leucine reduces the number of anxiety episodes in the PPD subject compared to prior to administration of the N-acetyl-leucine.
- [0113] The histopathological hallmark of PD is the presence of Lewy bodies (LBs), fibrillar aggregates in which α -synuclein is a major constituent. Pathological studies have shown a strong correlation between the extent of Lewy Body related cell loss in the Substantia Nigra (SN) and the severity of bradykinesia. Nigrostriatal dopaminergic damage can be monitored by functional neuroimaging techniques, such as positron emission tomography (PET) or single photon emission tomography (SPECT). (Meyer et al., *J Nuc Med*, 58(12), 1888-1898 (2017)).
- [0114] Molecular neuroimaging using PET allows for quantitative visualization of functional and molecular processes in vivo. The radiotracer 18F-2-fluoro-2-deoxy-D-glucose (18F-FDG) is a glucose analogue, and allows assessment of cerebral glucose metabolism in-vivo with positron emission tomography (PET). 18F-FDG is the most commonly used radiotracer for the assessment of regional cerebral glucose metabolism as a marker of neuronal function. By virtue of disclosing disease-specific alterations due to synaptic dysfunction, neuronal degeneration, and accompanying compensatory network changes, 18F-FDG PET has become an essential part in the diagnostic work-up of patients with neurodegenerative disorders. (Meyer et al., *J Nuc Med*, 58(12), 1888-1898 (2017)).
- [0115] Through 18F-FDG PET imaging, PD is characterized by a parietal, occipital, and sometimes frontal hypometabolism (especially in PD with cognitive impairment) and relative hypermetabolism of the putamen, pallidum, thalamus sensorimotor cortex, pons, and cerebellum. Conversely, MSA patients show a marked hypometabolism of the (posterior) putamen, pons, and cerebellum, which may be more pronounced in the striatum or in the pons and cerebellum, depending on the predominant side of degeneration and, thus, clinical presentation (striatonigral/MSA-P and olivopontocerebellar/MSA-C, respectively). An isolated cerebellar hypometabolism may

also occur in other causes of cerebellar degeneration (e.g., paraneoplastic or spinocerebellar ataxia). Group analyses demonstrated also a frontal hypometabolism that may spread to parietal and temporal areas simultaneously with the onset of cognitive impairment. The latter finding, however, is less apparent in individual analyses and of little help for differential diagnosis by 18F-FDG PET. (Meyer et al., J Nuc Med, 58(12), 1888-1898 (2017))

- [0116] In some embodiments, the PPD subject has reduced glucose metabolism in the parietal, occipital, and/or frontal regions of the brain. In some embodiments, the PPD subject has reduced glucose metabolism in one or more of the parietal, occipital, and/or frontal regions of the brain. In some embodiments, the PPD subject has reduced glucose metabolism in two or more of the parietal, occipital, and/or frontal regions of the brain. In some embodiments, the PPD subject has reduced glucose metabolism in the parietal, occipital, and frontal regions of the brain.
- [0117] In some embodiments, administering N-acetyl-leucine increases glucose metabolism in the brain of the PPD subject as compared to prior to administration of the N-acetyl-leucine. In some embodiments, administering N-acetyl-leucine increases glucose metabolism in the parietal, occipital, and/or frontal regions of the brain of the PPD subject compared to prior to the administration of N-acetyl leucine. In some embodiments, administering N-acetyl-leucine increases glucose metabolism in one or more of the parietal, occipital, and/or frontal regions of the brain of the PPD subject compared to prior to the administration of N-acetyl leucine.
- [0118] In some embodiments, the glucose metabolism is determined by a positron emission tomography (PET) scan. In some embodiments, the PET scan is a fluorodeoxyglucose-positron emission tomography (FDG-PET) scan. In some embodiments, the FDG-PET scan is used to generate the PPD subject's z-score.
- [0119] In some embodiments, administration of N-acetyl-leucine reduces the PPD subject's z-score. In some embodiments, administration of N-acetyl-leucine reduces the PPD subject's z-score in the parietal, occipital, and/or frontal regions of the brain. In some embodiments, the PPD subject's z-score is reduced by at least about 5%, about 10%, about 20%, about 30%, about 40%, or about least 50% compared to the PPD subject's z-score prior to administration of the N-acetyl-leucine.

- [0120] Neuronal loss in the Substantia Nigra pars compacta (SNc) associated with Lewy Body pathology is the pathologic hallmark feature of sporadic PD. Decreased nigrostriatal dopaminergic function is associated with nonmotor symptoms known to precede PD. Additionally, the extent of nigrostriatal dopaminergic denervation has been shown to correlate with severity of classical motor features of PD, in particular bradykinesia and rigidity. Nigrostriatal dopaminergic denervation can be shown using radiotracers that label presynaptic dopaminergic markers such as the striatal dopamine transporters (DAT) as routinely achieved with single photon emission computed tomography (SPECT) or decarboxylase activity with 18F-Dopa positron emission tomography (PET). (Mahlknecht et al., J Parkinson's Disease, 5, 681-697 (2015))
- [0121] 123I-ioflupane single-photon emission computed tomography (SPECT) assesses dopamine transporter (DAT) uptake in the basal ganglia *in vivo*. SPECT is a nuclear imaging modality that measures radioactivity of gamma rays emitted from radioactive compounds that are bound to tracers. By binding to the DAT, 123I-ioflupane allows imaging of the presynaptic terminal. DAT-SPECT provides a semiquantitative assessment of striatal dopaminergic deafferentation and is a well-established method for the assessment and investigation of PD. (Mahlknecht et al., J Parkinson's Disease, 5, 681-697 (2015))
- [0122] In patients with PD, DAT-SPECT shows decreased striatal DAT uptake, indicating substantia nigra dopaminergic dysfunction that is more marked in the putamen than in the caudate nucleus. The DAT deficit seen in RBD is less severe than in established PD suggesting that dopaminergic imaging may have the potential to quantify progression through the prodromal phase. 18F-Dopa PET studies in PD patients have shown faster rates of tracer-uptake decline in earlier versus later disease stages and, in accordance with the pathological post-mortem studies, extrapolation of these exponential curves have led to estimates of prediagnostic PD of approximately 6 years. (Hustad et al., Front. Neurol., 11:395 (2020)).
- [0123] In some embodiments, the PPD subject has decreased dopaminergic function in the basal ganglia. In some embodiments, the PPD subject has decreased DAT uptake in the basal ganglia. In some embodiments, the PPD subject has decreased DAT binding in the basal ganglia. In some embodiments, the PPD subject has decreased amounts of dopamine transporters in the basal ganglia.

[0124] In some embodiments, administration of N-acetyl-leucine increases the dopaminergic function in the PPD subject's basal ganglia compared to prior to administration of N-acetyl-leucine. In some embodiments, administration of N-acetyl-leucine increases the DAT uptake in the PPD subject's basal ganglia compared to prior to administration of N-acetyl-leucine. In some embodiments, administration of N-acetyl-leucine increases DAT binding in the PPD subject's basal ganglia compared to prior to administration of N-acetyl-leucine. In some embodiments, administration of N-acetyl-leucine increases the amount of dopamine transporters in the PPD subject's basal ganglia compared to prior to administration of N-acetyl-leucine.

[0125] In some embodiments, the amount of dopamine transporters in the PPD subject are determined by a dopamine transporter (DAT) scan. In some embodiments, the DAT scan is a DAT scan with single photon emission computed tomography (DAT-SPECT) or a DAT scan with decarboxylase activity with 18F-Dopa positron emission tomography (DAT-PET). In some embodiments, the DAT scan is a DAT-SPECT.

[0126] In 1995, Becker et al reported a highly characteristic enlargement of echogenic signal (hyperechogenicity) of the substantia nigra in idiopathic PD. Since then, a number of studies has been performed indicating that this method is a valuable tool for the differential diagnosis of PD, which even allows the identification of PPD subjects at risk for nigrostriatal dysfunction. (Pellicano et al., Neuropsychiatric Disease and Treatment, 3(1), 145-151 (2007)).

B. Dementia with Lewy bodies (DLB)

[0127] In some embodiments, the disclosure provides methods of treating the prodromal phase of DLB in a subject in need thereof comprising administering a therapeutically effective amount of N-acetyl-leucine to the subject. These subjects are referred to in this section as a "prodromal dementia with Lewy bodies subject" or "PDLB subject."

[0128] In some embodiments, the PDLB subject is not diagnosed with dementia. In some embodiments, the PDLB subject is not diagnosed with one or more of mild cognitive impairment (MCI), delirium-onset, and/or psychiatric-onset. In some embodiments, the PDLB subject is not diagnosed with dementia and is diagnosed with one or more of mild cognitive impairment (MCI), delirium-onset, and/or psychiatric-onset.

[0129] In some embodiments, the PDLB subject is not diagnosed with any of the core clinical features, syndromes, or symptoms associated with DLB. In some embodiments, the core clinical features, syndromes, or symptoms associated with DLB are dementia, parkinsonism, RBD, fluctuating cognition/alertness, and/or visual hallucinations. In some embodiments, the PDLB subject is not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations. In some embodiments, the PDLB subject is not diagnosed with dementia.

[0130] Dementia with Lewy bodies (DLB) is a common form of dementia in older people characterized by Lewy bodies consisting mainly of alpha-synuclein within the brain at postmortem of patients who had a clinical dementia syndrome. Dementia with lewy bodies (DLB) is characterized by dementia together with varying combinations of the core clinical features of parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations. The differentiation of patients with DLB from patients with Alzheimer’s dementia (AD) is often difficult for clinicians, especially as Alzheimer’s pathology can be present to varying degrees in DLB, affecting the clinical presentation and imaging findings. (McKeith et al., Neurology, 94(17), 743-755 (2020)).

[0131] In some embodiments, the PDLB subject is not diagnosed with dementia and at least two of the core features listed in Table 3. In some embodiments, the PDLB subject is not diagnosed with dementia, at least one core features listed in Table 3, and at least one indicative biomarker listed in Table 3.

Table 3.

Table Diagnostic Criteria for Dementia with Lewy Bodies (DLB)
(Surendranathan et al., Evid Based Menthal Health, 21(2), 61-65 (2018))

Diagnostic criteria
For a patients with dementia (defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions or with activities of daily living):
1. A ‘probable’ DLB diagnosis requires at least two core features or one core feature and at least one indicative biomarker, whereas
2. A ‘possible’ DLB diagnosis requires only one of the seven from the list of core features or indicative biomarkers.
Supportive biomarkers are helpful in making the diagnosis, but their specificity to DLB is not clear.

In addition, a patient must have either developed dementia below, or within 1 year, of the onset of any parkinsonian symptoms; hence, if more than a year passes before the onset of dementia following parkinsonism, the alternative diagnosis of Parkinson's disease dementia (PDD) is made.

Core features	Indicative biomarkers	Supportive biomarkers
1. recurrent visual hallucinations 2. fluctuating cognition 3. spontaneous features of parkinsonism 4. rapid eye movement (REM) sleep behaviour disorder (RBD).	1. polysomnography confirming RBD by showing REM sleep without atonia 2. abnormal dopamine transporter (DAT) imaging revealing reduced DAT uptake in the basal ganglia 3. ¹²³ Iodine-metaiodobenzylguanidine myocardial scintigraphy revealing loss of postganglionic sympathetic cardiac innervation.	1. relative preservation of medial temporal lobe structures on CT or MRI 2. generalized low uptake on single-photon emission CT/positron emission tomography (PET) perfusion/metabolism scan with reduced occipital activity ± posterior cingulate island sign on fluorodeoxyglucose PET imaging 3. prominent posterior slow-wave activity on EEG with periodic fluctuations in the prealpha/theta range.

[0132] Prodromal DLB refers to a predementia stage with signs or symptoms indicating that DLB will subsequently develop and encompasses not only cognitive deficits but also a variable mixture of noncognitive clinical features including motor symptoms and signs, sleep disorders, autonomic dysfunction, and neuropsychiatric disturbance. Specific markers of prodromal DLB include rapid eye movement (REM) sleep behavior disorder (RBD), olfactory dysfunction, autonomic dysfunction, depression, and diffuse occipital hypometabolism on FDG-PET. (McKeith et al., Neurology, 94(17), 743-755 (2020))

Table 4
Temporal Order of Symptom Development in Prodromal DLB
(Donaghy et al., Psy Med, 45, 259-268 (2015))

	Very early (developing before cognitive symptoms)	Early (developing during MCI)	Late (developing around the time of conversion to dementia or later)
Symptoms	RBD Constipation	Memory impairment	Cognitive fluctuations

Signs/neuropsychological findings/biomarkers	Hyposmia Depression <i>Urinary dysfunction</i> <i>Erectile dysfunction</i>	Parkinsonian symptoms Visual hallucinations Anxiety Attention/executive dysfunction Visuospatial dysfunction Striatal dopaminergic denervation <i>Substantia nigra hyperechogenicity</i> <i>Increased hippocampal rCBF</i>	Occipital hypometabolism
	Orthostatic hypotension/dizziness <i>Minor motor abnormalities</i> <i>Impaired olfactory function</i> <i>Impaired colour vision</i>		

DLB, Dementia with Lewy bodies; MCI, mild cognitive impairment; RBD, rapid eye movement (REM) sleep behaviour disorder; rCBF, region cerebral blood flow.
Items in italics reflect evidence from cohorts with RBD at baseline that may not be applicable to prodromal DLB as a whole.

[0133] In some embodiments, the PDLB subject is diagnosed with one or more core clinical features, syndromes, or symptoms associated with the prodromal phase of DLB. In some embodiments, the one or more core clinical features, syndromes, or symptoms associated with the prodromal phase of DLB are RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0134] In some embodiments, the PDLB subject is diagnosed with one or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

- [0135]** In some embodiments, the PDLB subject is diagnosed with two or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.
- [0136]** In some embodiments, the PDLB subject is diagnosed with three or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.
- [0137]** In some embodiments, the PDLB subject is diagnosed with four or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.
- [0138]** In some embodiments, the PDLB subject is diagnosed with five or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.
- [0139]** In some embodiments, the PDLB subject is diagnosed with six or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety,

mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

- [0140] In some embodiments, the PDLB subject is diagnosed with seven or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.
- [0141] In some embodiments, the PDLB subject is diagnosed with eight or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.
- [0142] In some embodiments, the PDLB subject is diagnosed with nine or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.
- [0143] In some embodiments, the PDLB subject is diagnosed with ten or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

- [0144] In some embodiments, the PDLB subject is diagnosed with eleven or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.
- [0145] In some embodiments, the PDLB subject is diagnosed with twelve or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.
- [0146] In some embodiments, the PDLB subject is diagnosed with thirteen or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.
- [0147] In some embodiments, the PDLB subject is diagnosed with fourteen or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.
- [0148] In some embodiments, the PDLB subject is diagnosed with fifteen or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual

hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0149] In some embodiments, the PDLB subject is diagnosed with sixteen or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0150] In some embodiments, the PDLB subject is diagnosed with seventeen or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0151] In some embodiments, the PDLB subject is diagnosed with eighteen or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0152] In some embodiments, the PDLB subject is diagnosed with nineteen or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

- [0153] In some embodiments, the PDLB subject is diagnosed with RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and increased hippocampal rCBF.
- [0154] In some embodiments, the one or more core clinical features, syndromes, or symptoms associated with the prodromal phase of DLB are RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.
- [0155] In some embodiments, the PDLB subject is diagnosed with one or more of RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.
- [0156] In some embodiments, the PDLB subject is diagnosed with two or more of RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.
- [0157] In some embodiments, the PDLB subject is diagnosed with three or more of RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.
- [0158] In some embodiments, the PDLB subject is diagnosed with four or more of RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.

- [0159] In some embodiments, the PDLB subject is diagnosed with five or more of RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.
- [0160] In some embodiments, the PDLB subject is diagnosed with six or more of RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.
- [0161] In some embodiments, the PDLB subject is diagnosed with seven or more of RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.
- [0162] In some embodiments, the PDLB subject is diagnosed with eight or more of RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.
- [0163] In some embodiments, the PDLB subject is diagnosed with nine or more of RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.
- [0164] In some embodiments, the PDLB subject is diagnosed with ten or more of RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.
- [0165] In some embodiments, the PDLB subject is diagnosed with eleven or more of RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory

impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.

[0166] In some embodiments, the PDLB subject is diagnosed with twelve or more of RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.

[0167] In some embodiments, the PDLB subject is diagnosed with constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and striatal dopaminergic denervation.

[0168] In some embodiments, the one or more core clinical features, syndromes, or symptoms associated with the prodromal phase of DLB are RBD, constipation, hyposmia, depression, and/or orthostatic hypotension/dizziness. In some embodiments, the PDLB subject is diagnosed with one or more of RBD, constipation, hyposmia, depression, and/or orthostatic hypotension/dizziness. In some embodiments, the PDLB subject is diagnosed with two or more of RBD, constipation, hyposmia, depression, and/or orthostatic hypotension/dizziness. In some embodiments, the PDLB subject is diagnosed with three or more of RBD, constipation, hyposmia, depression, and/or orthostatic hypotension/dizziness. In some embodiments, the PDLB subject is diagnosed with four or more of RBD, constipation, hyposmia, depression, and/or orthostatic hypotension/dizziness. In some embodiments, the PDLB subject is diagnosed with RBD, constipation, hyposmia, depression, and orthostatic hypotension/dizziness.

[0169] In some embodiments, the PDLB subject is: (i) not diagnosed with any of the core clinical features, syndromes, or symptoms associated with DLB and the PDLB subject is (ii) diagnosed with one or more core clinical features, syndromes, or symptoms associated with the prodromal phase of DLB. In some embodiments, the PDLB subject is: (i) not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with one or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic

hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0170] In some embodiments, the PDLB subject is: (i) not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with two or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0171] In some embodiments, the PDLB subject is: (i) not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with three or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0172] In some embodiments, the PDLB subject is: (i) not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with four or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0173] In some embodiments, the PDLB subject is: (i) not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with five or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0174] In some embodiments, the PDLB subject is: (i) not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with six or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0175] In some embodiments, the PDLB subject is: (i) not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with seven or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0176] In some embodiments, the PDLB subject is: (i) not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with eight or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory

impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0177] In some embodiments, the PDLB subject is: (i) not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with nine or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0178] In some embodiments, the PDLB subject is: (i) not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with ten or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0179] In some embodiments, the PDLB subject is: (i) not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with eleven or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0180] In some embodiments, the PDLB subject is: (i) not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with twelve or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0181] In some embodiments, the PDLB subject is: (i) not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with thirteen or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0182] In some embodiments, the PDLB subject is: (i) not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with fourteen or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0183] In some embodiments, the PDLB subject is: (i) not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with fifteen or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory

impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0184] In some embodiments, the PDLB subject is: (i) not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with sixteen or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0185] In some embodiments, the PDLB subject is: (i) not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with seventeen or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0186] In some embodiments, the PDLB subject is: (i) not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with eighteen or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

- [0187] In some embodiments, the PDLB subject is: (i) not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with nineteen or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.
- [0188] In some embodiments, the PDLB subject is: (i) not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and increased hippocampal rCBF.
- [0189] In some embodiments, the PDLB subject: (i) is not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with one or more core clinical features, syndromes, or symptoms associated with the prodromal phase of DLB are RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.
- [0190] In some embodiments, the PDLB subject: (i) is not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with two or more core clinical features, syndromes, or symptoms associated with the prodromal phase of DLB are RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.

- [0191] In some embodiments, the PDLB subject: (i) is not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with three or more core clinical features, syndromes, or symptoms associated with the prodromal phase of DLB are RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.
- [0192] In some embodiments, the PDLB subject: (i) is not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with four or more core clinical features, syndromes, or symptoms associated with the prodromal phase of DLB are RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.
- [0193] In some embodiments, the PDLB subject: (i) is not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with five or more core clinical features, syndromes, or symptoms associated with the prodromal phase of DLB are RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.
- [0194] In some embodiments, the PDLB subject: (i) is not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with six or more core clinical features, syndromes, or symptoms associated with the prodromal phase of DLB are RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.
- [0195] In some embodiments, the PDLB subject: (i) is not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with seven or more core clinical features, syndromes, or symptoms associated with the prodromal phase of DLB are RBD, constipation, hyposmia,

depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.

[0196] In some embodiments, the PDLB subject: (i) is not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with eight or more core clinical features, syndromes, or symptoms associated with the prodromal phase of DLB are RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.

[0197] In some embodiments, the PDLB subject: (i) is not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with nine or more core clinical features, syndromes, or symptoms associated with the prodromal phase of DLB are RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.

[0198] In some embodiments, the PDLB subject: (i) is not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with ten or more core clinical features, syndromes, or symptoms associated with the prodromal phase of DLB are RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.

[0199] In some embodiments, the PDLB subject: (i) is not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with eleven or more core clinical features, syndromes, or symptoms associated with the prodromal phase of DLB are RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.

- [0200] In some embodiments, the PDLB subject: (i) is not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (ii) diagnosed with twelve or more core clinical features, syndromes, or symptoms associated with the prodromal phase of DLB are RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.
- [0201] In some embodiments, the PDLB subject is: (i) not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (i) diagnosed with one or more of RBD, constipation, hyposmia, depression, and/or orthostatic hypotension/dizziness.
- [0202] In some embodiments, the PDLB subject is: (i) not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (i) diagnosed with two or more of RBD, constipation, hyposmia, depression, and/or orthostatic hypotension/dizziness.
- [0203] In some embodiments, the PDLB subject is: (i) not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (i) diagnosed with three or more of RBD, constipation, hyposmia, depression, and/or orthostatic hypotension/dizziness.
- [0204] In some embodiments, the PDLB subject is: (i) not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (i) diagnosed with four or more of RBD, constipation, hyposmia, depression, and/or orthostatic hypotension/dizziness.
- [0205] In some embodiments, the PDLB subject is: (i) not diagnosed with dementia, parkinsonism, RBD, fluctuating cognition/alertness, and visual hallucinations; and the PDLB subject is (i) diagnosed with RBD, constipation, hyposmia, depression, and orthostatic hypotension/dizziness.
- [0206] FDG-PET has found reduced regional glucose metabolism in the occipital association cortex and primary visual area in patients with DLB. The relative hypoperfusion in the occipital cortices has also been reported in patients with DLB. Involvement of the medial and lateral occipital lobes is unique to patients with DLB, and occipital hypometabolism and hypoperfusion are the features of DLB that discriminate it

from Alzheimer's disease (AD). (Ishii et al., *Annals of Nuc Med*, 18(5), 447-451 (2004); Kantarci et al., *NeuroImage: Clinical*, 31, 1-7 (2021))

[0207] In some embodiments, the PDLB subject has reduced glucose metabolism one or more of in the medial occipital lobes, lateral occipital lobes, occipital association cortex, and/or primary visual area of the brain. In some embodiments, the PDLB subject has reduced glucose metabolism in the medial occipital lobes, lateral occipital lobes, occipital association cortex, and primary visual area the brain.

[0208] In some embodiments, administering N-acetyl-leucine increases glucose metabolism in the brain of the PDLB subject as compared to prior to administration of the N-acetyl-leucine. In some embodiments, administering N-acetyl-leucine increases glucose metabolism in the medial occipital lobes, lateral occipital lobes, occipital association cortex, and/or primary visual area of the brain of the PDLB subject compared to prior to the administration of N-acetyl leucine. In some embodiments, administering N-acetyl-leucine increases glucose metabolism in the medial occipital lobes, lateral occipital lobes, occipital association cortex, and/or primary visual area of the brain of the PDLB subject compared to prior to the administration of N-acetyl leucine.

[0209] In some embodiments, the glucose metabolism is determined by a positron emission tomography (PET) scan. In some embodiments, the PET scan is a fluorodeoxyglucose-positron emission tomography (FDG-PET) scan. In some embodiments, the FDG-PET scan is used to generate the PDLB subject's z-score.

[0210] In some embodiments, administration of N-acetyl-leucine reduces the PDLB subject's z-score. In some embodiments, administration of N-acetyl-leucine reduces the PDLB subject's z-score in the medial occipital lobes, lateral occipital lobes, occipital association cortex, and/or primary visual area of the brain. In some embodiments, the PDLB subject's z-score is reduced by at least about 5%, about 10%, about 20%, about 30%, about 40%, or about least 50% compared to the PDLB subject's z-score prior to administration of the N-acetyl-leucine.

[0211] The utility of DAT scans particularly in differentiating DLB from AD is based on the reduction of dopamine terminals within the striatum seen in DLB, compared with their relative preservation in AD. However, DAT imaging can be abnormal in other degenerative disorders where dopaminergic transmission is affected, such as

frontotemporal dementia (FTD), corticobasal degeneration (CBD), progressive supranuclear palsy and multiple systems atrophy.

[0212] In some embodiments, the PDLB subject has decreased dopaminergic function in the basal ganglia. In some embodiments, the PDLB subject has decreased DAT uptake in the basal ganglia. In some embodiments, the PDLB subject has decreased DAT binding in the basal ganglia. In some embodiments, the PDLB subject has decreased amounts of dopamine transporters in the basal ganglia.

[0213] In some embodiments, administration of N-acetyl-leucine increases the dopaminergic function in the PDLB subject's basal ganglia compared to prior to administration of N-acetyl-leucine. In some embodiments, administration of N-acetyl-leucine increases the DAT uptake in the PDLB subject's basal ganglia compared to prior to administration of N-acetyl-leucine. In some embodiments, administration of N-acetyl-leucine increases DAT binding in the PDLB subject's basal ganglia compared to prior to administration of N-acetyl-leucine. In some embodiments, administration of N-acetyl-leucine increases the amount of dopamine transporters in the PDLB subject's basal ganglia compared to prior to administration of N-acetyl-leucine.

[0214] In some embodiments, the amount of dopamine transporters in the PDLB subject are determined by a dopamine transporter (DAT) scan. In some embodiments, the DAT scan is a DAT scan with single photon emission computed tomography (DAT-SPECT) or a DAT scan with decarboxylase activity with 18F-Dopa positron emission tomography (DAT-PET). In some embodiments, the DAT scan is a DAT-SPECT.

C. Multiple systems atrophy (MSA)

[0215] In some embodiments the disclosure provides methods of treating the prodromal phase of MSA in a subject in need thereof comprising administering a therapeutically effective amount of N-acetyl-leucine to the subject. These subjects are referred to in this section as a "prodromal multiple systems atrophy subject" or "PMSA subject."

[0216] In some embodiments, the PMSA subject is not diagnosed with (a) an autonomic dysfunction; and (b) L-dopa-responsive parkinsonism and/or cerebellar syndrome. In some embodiments, the PMSA subject is diagnosed with one or more of RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and/or

urogenital failure. In some embodiments, the PMSA subject is not diagnosed with (a) an autonomic dysfunction; and (b) poorly L-dopa-responsive parkinsonism and/or cerebellar syndrome; and is diagnosed with one or more of RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and/or urogenital failure.

[0217] Multiple systems atrophy (MSA) is an adult-onset neurodegenerative disease characterized by a combination of parkinsonism, autonomic disorder, and cerebellar ataxia. Based on the predominant symptoms of the disease, MSA is categorized into two forms of MSA: MSA with predominant Parkinsonism (MSA-P) and MSA with predominant cerebellar features (MSA-C). Age at onset, prevalence of cardiovascular autonomic dysfunction, sleep disorders, and retinal abnormalities are similar in both phenotypes. Specific neuroimaging markers differ between the cerebellar and parkinsonian phenotypes as well as the degree of sudomotor dysfunction which may be more severe in patients with MSA-P and urogenital dysfunction which may occur earlier in patients with MSA-C. (Palma et al., Auton Neurosci, 211: 15-25 (2018))

[0218] While in patients with Parkinson disease (PD) α Syn predominantly accumulates in neurons forming Lewy bodies and Lewy neurites, in patients with MSA it accumulates mostly in oligodendroglial cells forming glial cytoplasmic inclusions (GCI). A significant percentage of patients with MSA present with genitourinary dysfunction and orthostatic hypotension (OH) due to dysfunction of the autonomic nervous system, frequently combined with a history suggesting rapid eye movement (REM) sleep behavior disorder (RBD). (Palma et al., Auton Neurosci, 211: 15-25 (2018)) The criteria for diagnosis of MSA is shown in Table 5.

Table 5

Criteria for Diagnosis of MSA

(Palma et al., Auton Neurosci, 211: 15-25 (2018))

Criteria for definite MSA include neuropathological findings during postmortem examination of:
a) Widespread and abundant cerebral α -synuclein-positive glial cytoplasmic inclusions
b) Neurodegenerative changes in striatonigral or olivopontocerebellar region
Criteria for probably MSA include a sporadic progressive adult (> 30 years old)-onset disease characterized by:

a) Autonomic failure involving urinary incontinence (inability to control the release of urine from the bladder with erectile dysfunction in males) or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mmHg systolic or 15 mmHg diastolic, <i>and</i>
b) Poorly levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor or postural instability), <i>or</i>
c) A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia or cerebellar oculomotor dysfunction)
Criteria for possible MSA include a sporadic progressive adult (> 30 years old)-onset disease characterized by:
a) Parkinsonism (bradykinesia with rigidity tremor or postural instability), <i>or</i>
b) Cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia or cerebellar oculomotor dysfunction), <i>and</i>
c) At least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency frequency or incomplete bladder emptying, erectile dysfunction in males, or significant orthostatic BP decline that does not meet the level required in probable MSA), <i>and</i>
d) At least one of the following features: • Babinski sign with hyperreflexia • Stridor • Rapidly progressive parkinsonism • Poor response to levodopa • Postural instability within 3 years of motor onset • Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction • Dysphagia within 5 years of motor onset • Atrophy on MRI of putamen middle cerebellar peduncle, pons or cerebellum • Hypometabolism on FDG-PET in putamen, brainstem or cerebellum • Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET

[0219] In some embodiments, the PMSA subject is not diagnosed with any of the core clinical features, syndromes, or symptoms associated with MSA. In some embodiments, the core clinical features, syndromes, or symptoms associated with MSA are widespread and abundant cerebral alpha-synuclein-positive glial cytoplasmic inclusions, neurodegenerative changes in the striatonigral or olivopontocerebellar region, urinary incontinence, orthostatic decrease of blood pressure, poorly levodopa-responsive parkinsonism, a cerebellar syndrome, and/or parkinsonism. In some embodiments, the PMSA subject is not diagnosed with widespread and abundant cerebral alpha-synuclein-positive glial cytoplasmic inclusions, neurodegenerative changes in the striatonigral or olivopontocerebellar region, urinary incontinence, orthostatic decrease of blood pressure, poorly levodopa-responsive parkinsonism, a cerebellar syndrome, and/or parkinsonism.

[0220] In some embodiments, the core clinical features, syndromes, or symptoms associated with MSA are widespread and abundant cerebral alpha-synuclein-positive glial

cytoplasmic inclusions and/or neurodegenerative changes in the striatonigral or olivopontocerebellar region. In some embodiments, the PMSA subject is not diagnosed with widespread and abundant cerebral alpha-synuclein-positive glial cytoplasmic inclusions and/or neurodegenerative changes in the striatonigral or olivopontocerebellar region.

[0221] In some embodiments, the core clinical features, syndromes, or symptoms associated with MSA are urinary incontinence or orthostatic decrease of blood pressure; and poorly levodopa-responsive parkinsonism or a cerebellar syndrome. In some embodiments, the PMSA subject is not diagnosed with urinary incontinence or orthostatic decrease of blood pressure; and poorly levodopa-responsive parkinsonism or a cerebellar syndrome.

[0222] In some embodiments, the core clinical features, syndromes, or symptoms associated with MSA are parkinsonism or cerebellar syndrome; and autonomic dysfunction. In some embodiments, the PMSA subject is not diagnosed with parkinsonism or cerebellar syndrome; and autonomic dysfunction.

[0223] In some embodiments, symptoms of the poorly levodopa-responsive parkinsonism are bradykinesia with rigidity, tremor, and/or postural instability. In some embodiments, symptoms of cerebellar syndrome are gait ataxia with cerebellar dysarthria, limb ataxia, and/or cerebellar oculomotor dysfunction. In some embodiments, the symptoms of parkinsonism are bradykinesia with rigidity tremor and/or postural instability.

Table 6

Criteria for Prodromal MSA

(Wenning et al., Movement Disorders, 37(6), 1131-1148 (2022))

Essential features	A sporadic, progressive adult (>30 years) onset disease
Clinical non-motor features (entry criteria)	At least one of the following: - RBD (polysomnography proven) - Neurogenic OH ($\geq 20/10$ mmHg blood pressure drop) within 10 minutes of standing or head-up tilt - Urogenital failure (erectile dysfunction in males below age of 60 years combined with at least one of unexplained voiding

	difficulties with post-void urinary residual volume >100 mL and unexplained urinary urge incontinence)
Clinical motor features	At least one of the following: - Subtle parkinsonian signs - Subtle cerebellar signs
Exclusion criteria	- At least one of unexplained anosmia on olfactory testing or abnormal cardiac sympathetic imaging (123I-MIBG-scintigraphy) - Fluctuating cognition with pronounced variation in attention and alertness and early decline in visuoperceptual abilities - Recurrent visual hallucinations not induced by drugs within 3 years of disease onset - Dementia according to DSM-V within 3 years of disease onset - Downgaze supranuclear gaze palsy or slowing of vertical saccades - Brain MRI findings suggestive of an alternative diagnosis (eg, PSP, multiple sclerosis, vascular parkinsonism, symptomatic cerebellar disease, etc.) - Documentation of an alternative condition (MSA look-alike, including genetic or symptomatic ataxia and parkinsonism) known to produce autonomic failure, ataxia, or parkinsonism and plausibly connected to the patient's symptoms

[0224] In some embodiments, the PMSA subject is diagnosed with one or more core clinical features, syndromes, or symptoms associated with the prodromal phase of MSA. In some embodiments, the core clinical features, syndromes, or symptoms associated with the prodromal phase of MSA are RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and/or urogenital failure. In some embodiments, the PMSA subject is diagnosed with one or more of RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and/or urogenital failure. In some embodiments, the PMSA subject is diagnosed with two or more of RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and/or urogenital

failure. In some embodiments, the PMSA subject is diagnosed with RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and urogenital failure.

[0225] In some embodiments, the PMSA subject: (i) is not diagnosed with any of the core clinical features, syndromes, or symptoms associated with MSA and is (ii) diagnosed with one or more of the core clinical features, syndromes, or symptoms associated with the prodromal phase of MSA.

[0226] In some embodiments, the PMSA subject is: (i) not diagnosed with widespread and abundant cerebral alpha-synuclein-positive glial cytoplasmic inclusions, neurodegenerative changes in the striatonigral or olivopontocerebellar region, urinary incontinence, orthostatic decrease of blood pressure, poorly levodopa-responsive parkinsonism, a cerebellar syndrome, and/or parkinsonism; and is (ii) diagnosed with one or more of RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and/or urogenital failure.

[0227] In some embodiments, the PMSA subject is: (i) not diagnosed with widespread and abundant cerebral alpha-synuclein-positive glial cytoplasmic inclusions, neurodegenerative changes in the striatonigral or olivopontocerebellar region, urinary incontinence, orthostatic decrease of blood pressure, poorly levodopa-responsive parkinsonism, a cerebellar syndrome, and/or parkinsonism; and is (ii) diagnosed with two or more of RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and/or urogenital failure.

[0228] In some embodiments, the PMSA subject is: (i) not diagnosed with widespread and abundant cerebral alpha-synuclein-positive glial cytoplasmic inclusions, neurodegenerative changes in the striatonigral or olivopontocerebellar region, urinary incontinence, orthostatic decrease of blood pressure, poorly levodopa-responsive parkinsonism, a cerebellar syndrome, and/or parkinsonism; and is (ii) diagnosed with RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and urogenital failure.

[0229] In some embodiments, the PMSA subject is: (i) not diagnosed with widespread and abundant cerebral alpha-synuclein-positive glial cytoplasmic inclusions and/or neurodegenerative changes in the striatonigral or olivopontocerebellar region; and is (ii)

diagnosed with one or more of RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and/or urogenital failure.

[0230] In some embodiments, the PMSA subject is: (i) not diagnosed with widespread and abundant cerebral alpha-synuclein-positive glial cytoplasmic inclusions and/or neurodegenerative changes in the striatonigral or olivopontocerebellar region; and is (ii) diagnosed with two or more of RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and/or urogenital failure.

[0231] In some embodiments, the PMSA subject is: (i) not diagnosed with widespread and abundant cerebral alpha-synuclein-positive glial cytoplasmic inclusions and/or neurodegenerative changes in the striatonigral or olivopontocerebellar region; and is (ii) diagnosed with RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and urogenital failure.

[0232] In some embodiments, the PMSA subject: (i) is not diagnosed with urinary incontinence or orthostatic decrease of blood pressure; and poorly levodopa-responsive parkinsonism or a cerebellar syndrome; and is (ii) diagnosed with one or more of RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and/or urogenital failure.

[0233] In some embodiments, the PMSA subject: (i) is not diagnosed with urinary incontinence or orthostatic decrease of blood pressure; and poorly levodopa-responsive parkinsonism or a cerebellar syndrome; and is (ii) diagnosed with two or more of RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and/or urogenital failure.

[0234] In some embodiments, the PMSA subject: (i) is not diagnosed with urinary incontinence or orthostatic decrease of blood pressure; and poorly levodopa-responsive parkinsonism or a cerebellar syndrome; and is (ii) diagnosed with RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and urogenital failure.

[0235] In some embodiments, the PMSA subject: (i) is not diagnosed with parkinsonism or cerebellar syndrome; and autonomic dysfunction; and is (ii) diagnosed with one or more of RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and/or urogenital failure.

- [0236] In some embodiments, the PMSA subject: (i) is not diagnosed with parkinsonism or cerebellar syndrome; and autonomic dysfunction; and is (ii) diagnosed with two or more of RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and/or urogenital failure.
- [0237] In some embodiments, the PMSA subject: (i) is not diagnosed with parkinsonism or cerebellar syndrome; and autonomic dysfunction; and is (ii) diagnosed with RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and/or urogenital failure. MSA patients show a marked hypometabolism of the (posterior) putamen, pons, caudate, and cerebellum, which may be more pronounced in the striatum or in the pons and cerebellum, depending on the predominant side of degeneration and, thus, clinical presentation (striatonigral/MSA-P and olivopontocerebellar/MSA-C, respectively).
- [0238] In some embodiments, the PMSA subject has reduced glucose metabolism in the putamen, pons, caudate, and/or cerebellum. In some embodiments, the PMSA subject has reduced glucose metabolism in one or more of the putamen, pons, caudate, and/or cerebellum.
- [0239] In some embodiments, administering N-acetyl-leucine increases glucose metabolism in the brain of the PMSA subject as compared to prior to administration of the N-acetyl-leucine. In some embodiments, administering N-acetyl-leucine increases glucose metabolism in the putamen, pons, caudate, and/or cerebellum of the PMSA subject compared to prior to the administration of N-acetyl leucine. In some embodiments, administering N-acetyl-leucine increases glucose metabolism in one or more of the putamen, pons, caudate, and/or cerebellum of the PMSA subject compared to prior to the administration of N-acetyl leucine.
- [0240] The most characteristic finding in patients with MSA-P is a reduction in 18FDGPET uptake in both putamen nuclei with a rostrocaudal gradient. This finding has a sensitivity of ~95% and a specificity of 100% to distinguish PD vs. MSA-P. Decreased 18FDG-PET uptake can also be detected in the thalamus, brainstem and cortical areas. Thus, current consensus diagnostic criteria for MSA established hypometabolism in the putamen nucleus, mesencephalic region and cerebellum as supportive for MSA-P. In patients with MSA-C, hypometabolism of the anterior cerebellar hemispheres and the vermis may be seen 1-year after the onset of motor symptoms, although hypometabolism

of the putamen can also be observed and is a supportive feature for the diagnosis of MSA-C. (Palma et al., *Auton Neurosci*, 211: 15-25 (2018); Jellinger K., *Annals of Indian Acad Neurol*, (2021); Zhao et al., *Brain and Behavior*, 1-9 (2020))

[0241] In some embodiments, the PMSA subject has reduced glucose metabolism in the putamen nuclei, thalamus, brainstem, mesencephalic region, cerebellum, anterior cerebellar hemispheres, the vermis, and cortical areas. In some embodiments, the PMSA subject has reduced glucose metabolism in the putamen nucleus, mesencephalic region and cerebellum. In some embodiments, the PMSA subject has reduced glucose metabolism in the putamen nuclei, anterior cerebellar hemispheres, and/or the vermis. In some embodiments, the PMSA subject has reduced glucose metabolism in the putamen nuclei. In some embodiments, the PMSA subject has reduced glucose metabolism in the anterior cerebellar hemispheres and the vermis.

[0242] In some embodiments, administration of N-acetyl-leucine increases glucose metabolism in the PMSA subject's putamen nuclei, thalamus, brainstem, mesencephalic region, cerebellum, anterior cerebellar hemispheres, the vermis, and cortical areas compared to prior to administration of N-acetyl-leucine. In some embodiments, administration of N-acetyl-leucine increases glucose metabolism in the PMSA subject's putamen nucleus, mesencephalic region and cerebellum compared to prior to administration of N-acetyl-leucine. In some embodiments, administration of N-acetyl-leucine increases glucose metabolism in the PMSA subject's putamen nuclei, anterior cerebellar hemispheres, and/or the vermis compared to prior to administration of N-acetyl-leucine. In some embodiments, administration of N-acetyl-leucine increases glucose metabolism in the PMSA subject's putamen nuclei compared to prior to administration of N-acetyl-leucine. In some embodiments, administration of N-acetyl-leucine increases glucose metabolism in the PMSA subject's anterior cerebellar hemispheres and the vermis compared to prior to administration of N-acetyl-leucine.

[0243] In some embodiments, glucose metabolism is determined by a positron emission tomography (PET) scan. In some embodiments, the PET scan is a fluorodeoxyglucose-positron emission tomography (FDG-PET) scan. In some embodiments, the FDG-PET scan is used to generate the PMSA subject's z-score.

[0244] In some embodiments, administration of N-acetyl-leucine reduces the PMSA subject's z-score. In some embodiments, administration of N-acetyl-leucine reduces the

PMSA subject's z-score in the putamen nuclei, anterior cerebellar hemispheres, and/or the vermis. In some embodiments, the PMSA subject's z-score is reduced by at least about 5%, about 10%, about 20%, about 30%, about 40%, or about least 50% compared to the PMSA subject's z-score prior to administration of the N-acetyl-leucine.

[0245] In some embodiments, the PMSA subject has decreased dopaminergic function in the basal ganglia. In some embodiments, the PMSA subject has decreased DAT uptake in the basal ganglia. In some embodiments, the PMSA subject has decreased DAT binding in the basal ganglia. In some embodiments, the PMSA subject has decreased amounts of dopamine transporters in the basal ganglia.

[0246] In some embodiments, administration of N-acetyl-leucine increases the dopaminergic function in the PMSA subject's basal ganglia compared to prior to administration of N-acetyl-leucine. In some embodiments, administration of N-acetyl-leucine increases the DAT uptake in the PMSA subject's basal ganglia compared to prior to administration of N-acetyl-leucine. In some embodiments, administration of N-acetyl-leucine increases DAT binding in the PMSA subject's basal ganglia compared to prior to administration of N-acetyl-leucine. In some embodiments, administration of N-acetyl-leucine increases the amount of dopamine transporters in the PMSA subject's basal ganglia compared to prior to administration of N-acetyl-leucine.

[0247] In some embodiments, the amount of dopamine transporters in the PMSA subject are determined by a dopamine transporter (DAT) scan. In some embodiments, the DAT scan is a DAT scan with single photon emission computed tomography (DAT-SPECT) or a DAT scan with decarboxylase activity with 18F-Dopa positron emission tomography (DAT-PET). In some embodiments, the DAT scan is a DAT-SPECT.

III. REM-Sleep Behavior Disorder (RBD)

[0248] In some embodiments the disclosure provides methods of treating RBD in a subject in need thereof, the method comprising administering a therapeutically effective amount of N-acetyl-leucine to the subject. In some embodiments, the RBD is idiopathic RBD. These subjects are referred to in this section as a "RBD subject."

[0249] REM-sleep behavior disorder (RBD) is a parasomnia characterized by dream-enacting behavior typically involving vocalizations or movements of the upper extremities, related to unpleasant dreams and loss of normal REM-sleep muscle atonia.

Rapid eye movement sleep behavior disorder is idiopathic when unassociated with neurological disorders or symptomatic when underlying causes such as autoimmune or inflammatory disorders, brain lesions, or provoking antidepressant medications are present. In both idiopathic and symptomatic categories, RBD is strongly associated with neurodegenerative diseases, especially synucleinopathies including PD, dementia with Lewy bodies (DLB), multiple system atrophy (MSA), and pure autonomic failure. (Claassen et al., *Neurology*, 75, 494-499 (2010))

[0250] Rapid eye movement sleep behavior disorder may manifest initially as an idiopathic prodromal state that occurs years to decades before the evolution of overt motor, cognitive, or autonomic impairments as the presenting manifestation of synucleinopathy. Dream enactment symptoms and idiopathic RBD diagnosis may be accompanied by other subtle prodromal features such as subjective cognitive symptoms without evidence of impairment on neuropsychological testing, asymptomatic cognitive or motor deficits, hyposmia, constipation, and orthostatic hypotension; many of these features are associated with a higher risk of pheno-conversion to a defined neurodegenerative disorder. The first study to document the relationship of RBD and these neurodegenerative disorders reported that nearly 40% of patients with isolated, idiopathic RBD later went on to develop a parkinsonian disorder after a mean of 12.7 years. Subsequent series have confirmed similar findings, with typical mean intervals from RBD to PD, DLB, or MSA around a decade. (St. Louis, et al., *Mayo Clin Proc.*, 92(11), 1723-1736 (2017))

[0251] Diagnosis of RBD requires either a clinical history of sleep-related complex motor behaviors or REM sleep complex vocal or motor behaviors recorded during polysomnography, accompanied by REM sleep without atonia (RSWA). Rapid eye movement sleep behavior disorder diagnosis also requires that the sleep disturbance is not better explained by another disorder, such as obstructive sleep apnea or an alternative non-rapid eye movement (NREM) sleep parasomnia. Idiopathic RBD is diagnosed when there is clinical sleep-related complex motor dream enactment behavior, without a clearly associated underlying pathology, such as PD or related synucleinopathies. Even when idiopathic, RBD has a very strong association with PD and other synucleinopathies. Rapid eye movement sleep behavior disorder is considered symptomatic RBD when it occurs in direct association with previously diagnosed PD, DLB, or MSA, or when there

is another known underlying pathology such as a brain lesion. (St. Louis, et al., Mayo Clin Proc., 92(11), 1723-1736 (2017)).

[0252] Patient-reported questionnaires have been developed for identification of individuals with RBD, but similarly to patients with hyposmia, patients with RBD are often not aware of their symptoms. Accurate collateral history from a bed partner is usually necessary to make the diagnosis. In questionable cases or for individuals without bed partners, polysomnography can be obtained. Cohort studies indicate that iRBD convert to PD and other synucleinopathies such as dementia with Lewy bodies and multiple systems atrophy. In some embodiments, the subject is diagnosed with RBD. (Meles et al., Mol Med, 27:111, 1-14 (2021)).

[0253] In some embodiments, the RBD subject has been diagnosed with prodromal Parkinson's disease (PPD), prodromal dementia with Lewy bodies (PDLB), or prodromal multiple systems atrophy (PMSA). In some embodiments, the RBD subject has not been diagnosed with classical or prodromal Parkinson's disease (PD), classical or prodromal dementia with Lewy bodies (DLB), or classical or prodromal multiple systems atrophy (MSA). In some embodiments, the RBD subject has not been diagnosed with Parkinson's disease, dementia with Lewy bodies, or multiple systems atrophy.

[0254] In some embodiments, the RBD subject is not diagnosed with any of the core clinical features, syndromes, or symptoms associated with Parkinson's Disease, dementia with Lewy bodies, or multiple systems atrophy. In some embodiments, the RBD subject has not been diagnosed with any of the core clinical features, syndromes, or symptoms associated with Parkinson's Disease, dementia with Lewy bodies, or multiple systems atrophy.

[0255] In some embodiments, the RBD subject is not diagnosed with any of the core clinical features, syndromes, or symptoms associated with Parkinson's disease. In some embodiments, the core clinical features, syndromes, or symptoms associated with Parkinson's disease are tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination. In some embodiments, the RBD subject is not diagnosed with one or more of tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination. In some embodiments, the RBD subject is not diagnosed with two more of tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination. In some embodiments, the RBD subject is not diagnosed with three more of tremor,

bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination. In some embodiments, the RBD subject is not diagnosed with four more of tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination. In some embodiments, the RBD subject is not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and impaired coordination.

- [0256] In some aspects, the RBD subject is not diagnosed with any of the core clinical features, syndromes, or symptoms associated with the prodromal phase of Parkinson's disease.
- [0257] In some aspects, the RBD subject is diagnosed with any of the core clinical features, syndromes, or symptoms associated with the prodromal phase of Parkinson's disease. In some aspects, the core clinical features, syndromes, or symptoms associated with the prodromal phase of Parkinson's disease are RBD, hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).
- [0258] In some embodiments, the RBD subject is diagnosed with one or more of RBD, hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).
- [0259] In some embodiments, the RBD subject is diagnosed with two or more of RBD, hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).
- [0260] In some embodiments, the RBD subject is diagnosed with three or more of RBD, hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

- [0261] In some embodiments, the RBD subject is diagnosed with four or more of RBD, hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).
- [0262] In some embodiments, the RBD subject is diagnosed with five or more of RBD, hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).
- [0263] In some embodiments, the RBD subject is diagnosed with six or more of RBD, hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).
- [0264] In some embodiments, the RBD subject is diagnosed with seven or more of RBD, hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).
- [0265] In some embodiments, the RBD subject is diagnosed with eight or more of RBD, hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).
- [0266] In some embodiments, the RBD subject is diagnosed with nine or more of RBD, hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).
- [0267] In some embodiments, the RBD subject is diagnosed with ten or more of RBD, hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety,

anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0268] In some embodiments, the RBD subject is diagnosed eleven one or more RBD, hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0269] In some embodiments, the RBD subject is diagnosed with twelve or more of RBD, hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0270] In some embodiments, the RBD subject is diagnosed with thirteen or more of RBD, hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0271] In some embodiments, the RBD subject is diagnosed with fourteen or more of RBD, hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0272] In some embodiments, the RBD subject is diagnosed with fifteen or more of RBD, hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction, excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0273] In some embodiments, the RBD subject is diagnosed with RBD, hyposmia, visual abnormalities, reduced color vision, pain, depression, anxiety, anhedonia, apathy, frontal executive dysfunction, constipation, orthostatic hypotension, urogenital dysfunction,

excessive daytime somnolence, sleep fragmentation, insomnia, periodic limb movements during sleep (PLMS), and/or restless leg syndrome (RLS).

[0274] In some embodiments, the core clinical features, syndromes, or symptoms associated with the prodromal phase of Parkinson's disease are RBD, hyposmia, cognitive impairment, constipation, depression, and anxiety. In some embodiments, the RBD subject is diagnosed with one or more of RBD, hyposmia, cognitive impairment, constipation, depression, and/or anxiety. In some embodiments, the RBD subject is diagnosed with two or more of RBD, hyposmia, cognitive impairment, constipation, depression, and/or anxiety. In some embodiments, the RBD subject is diagnosed with three or more of RBD, hyposmia, cognitive impairment, constipation, depression, and/or anxiety. In some embodiments, the RBD subject is diagnosed with four or more of RBD, hyposmia, cognitive impairment, constipation, depression, and/or anxiety. In some embodiments, the RBD subject is diagnosed with RBD, hyposmia, cognitive impairment, constipation, depression, and anxiety.

[0275] In some embodiments, the RBD subject is diagnosed with one or more of RBD, hyposmia and/or constipation. In some embodiments, the RBD subject is diagnosed with RBD, hyposmia and constipation.

[0276] In some embodiments, the RBD subject is not diagnosed with one or more core clinical features, syndromes, or symptoms associated with dementia with Lewy bodies (DLB). In some embodiments, the one or more core clinical features, syndromes, or symptoms associated with DLB are mild cognitive impairment (MCI), delirium-onset, and/or psychiatric-onset.

[0277] In some aspects, the RBD subject is not diagnosed with dementia. In some embodiments, the RBD subject is not diagnosed with one or more of mild cognitive impairment (MCI), delirium-onset, and/or psychiatric-onset. In some embodiments, the RBD subject is not diagnosed with dementia and is diagnosed with one or more of mild cognitive impairment (MCI), delirium-onset, and/or psychiatric-onset.

[0278] In some embodiments, the RBD subject is not diagnosed with any of the core clinical features, syndromes, or symptoms associated with DLB. In some embodiments, the core clinical features, syndromes, or symptoms associated with DLB are dementia, parkinsonism, fluctuating cognition/alertness, and/or visual hallucinations. In some

embodiments, the RBD subject is not diagnosed with dementia, parkinsonism, fluctuating cognition/alertness, and visual hallucinations.

[0279] In some embodiments, the RBD subject is not diagnosed with one or more core clinical features, syndromes, or symptoms associated with the prodromal phase of DLB.

[0280] In some embodiments, the RBD subject is diagnosed with one or more core clinical features, syndromes, or symptoms associated with the prodromal phase of DLB. In some embodiments, the one or more core clinical features, syndromes, or symptoms associated with the prodromal phase of DLB are RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0281] In some embodiments, the RBD subject is diagnosed with one or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0282] In some embodiments, the RBD subject is diagnosed with two or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0283] In some embodiments, the RBD subject is diagnosed with three or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety,

mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0284] In some embodiments, the RBD subject is diagnosed with four or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0285] In some embodiments, the RBD subject is diagnosed with five or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0286] In some embodiments, the RBD subject is diagnosed with six or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0287] In some embodiments, the RBD subject is diagnosed with seven or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

- [0288] In some embodiments, the RBD subject is diagnosed with eight or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.
- [0289] In some embodiments, the RBD subject is diagnosed with nine or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.
- [0290] In some embodiments, the RBD subject is diagnosed with ten or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.
- [0291] In some embodiments, the RBD subject is diagnosed with eleven or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.
- [0292] In some embodiments, the RBD subject is diagnosed with twelve or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual

hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0293] In some embodiments, the RBD subject is diagnosed with thirteen or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0294] In some embodiments, the RBD subject is diagnosed with fourteen or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0295] In some embodiments, the RBD subject is diagnosed with fifteen or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

[0296] In some embodiments, the RBD subject is diagnosed with sixteen or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.

- [0297] In some embodiments, the RBD subject is diagnosed with seventeen or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.
- [0298] In some embodiments, the RBD subject is diagnosed with eighteen or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.
- [0299] In some embodiments, the RBD subject is diagnosed with nineteen or more of RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and/or increased hippocampal rCBF.
- [0300] In some embodiments, the RBD subject is diagnosed with RBD, constipation, hyposmia, depression, urinary dysfunction, erectile dysfunction, orthostatic hypotension/dizziness, minor motor abnormalities, impaired olfactory function, impaired color vision, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, striatal dopaminergic denervation, substantia nigra hyperechogenicity, and increased hippocampal rCBF.
- [0301] In some embodiments, the one or more core clinical features, syndromes, or symptoms associated with the prodromal phase of DLB are RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian

symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.

[0302] In some embodiments, the RBD subject is diagnosed with one or more of RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.

[0303] In some embodiments, the RBD subject is diagnosed with two or more of RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.

[0304] In some embodiments, the RBD subject is diagnosed with three or more of RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.

[0305] In some embodiments, the RBD subject is diagnosed with four or more of RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.

[0306] In some embodiments, the RBD subject is diagnosed with five or more of RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.

[0307] In some embodiments, the RBD subject is diagnosed with six or more of RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.

- [0308] In some embodiments, the RBD subject is diagnosed with seven or more of RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.
- [0309] In some embodiments, the RBD subject is diagnosed with eight or more of RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.
- [0310] In some embodiments, the RBD subject is diagnosed with nine or more of RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.
- [0311] In some embodiments, the RBD subject is diagnosed with ten or more of RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.
- [0312] In some embodiments, the RBD subject is diagnosed with eleven or more of RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.
- [0313] In some embodiments, the RBD subject is diagnosed with twelve or more of RBD, constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and/or striatal dopaminergic denervation.
- [0314] In some embodiments, the RBD subject is diagnosed with constipation, hyposmia, depression, orthostatic hypotension/dizziness, memory impairment, parkinsonian

symptoms, visual hallucinations, anxiety, mild cognitive impairment, attention/executive dysfunction, visuospatial dysfunction, and striatal dopaminergic denervation.

[0315] In some embodiments, the one or more core clinical features, syndromes, or symptoms associated with the prodromal phase of DLB are RBD, constipation, hyposmia, depression, and/or orthostatic hypotension/dizziness. In some embodiments, the RBD subject is diagnosed with one or more of RBD, constipation, hyposmia, depression, and/or orthostatic hypotension/dizziness. In some embodiments, the RBD subject is diagnosed with two or more of RBD, constipation, hyposmia, depression, and/or orthostatic hypotension/dizziness. In some embodiments, the RBD subject is diagnosed with three or more of RBD, constipation, hyposmia, depression, and/or orthostatic hypotension/dizziness. In some embodiments, the RBD subject is diagnosed with four or more of RBD, constipation, hyposmia, depression, and/or orthostatic hypotension/dizziness. In some embodiments, the RBD subject is diagnosed with RBD, constipation, hyposmia, depression, and orthostatic hypotension/dizziness.

[0316] In some embodiments, the RBD subject is not diagnosed with any of the core clinical features, syndromes, or symptoms associated with MSA. In some embodiments, the core clinical features, syndromes, or symptoms associated with MSA are widespread and abundant cerebral alpha-synuclein-positive glial cytoplasmic inclusions, neurodegenerative changes in the striatonigral or olivopontocerebellar region, urinary incontinence, orthostatic decrease of blood pressure, poorly levodopa-responsive parkinsonism, a cerebellar syndrome, and/or parkinsonism. In some embodiments, the RBD subject is not diagnosed with widespread and abundant cerebral alpha-synuclein-positive glial cytoplasmic inclusions, neurodegenerative changes in the striatonigral or olivopontocerebellar region, urinary incontinence, orthostatic decrease of blood pressure, poorly levodopa-responsive parkinsonism, a cerebellar syndrome, and/or parkinsonism.

[0317] In some embodiments, the core clinical features, syndromes, or symptoms associated with MSA are widespread and abundant cerebral alpha-synuclein-positive glial cytoplasmic inclusions and/or neurodegenerative changes in the striatonigral or olivopontocerebellar region. In some embodiments, the RBD subject is not diagnosed with widespread and abundant cerebral alpha-synuclein-positive glial cytoplasmic inclusions and/or neurodegenerative changes in the striatonigral or olivopontocerebellar region.

- [0318] In some embodiments, the core clinical features, syndromes, or symptoms associated with MSA are urinary incontinence or orthostatic decrease of blood pressure; and poorly levodopa-responsive parkinsonism or a cerebellar syndrome. In some embodiments, the RBD subject is not diagnosed with urinary incontinence or orthostatic decrease of blood pressure; and poorly levodopa-responsive parkinsonism or a cerebellar syndrome.
- [0319] In some embodiments, the core clinical features, syndromes, or symptoms associated with MSA are parkinsonism or cerebellar syndrome; and autonomic dysfunction. In some embodiments, the RBD subject is not diagnosed with parkinsonism or cerebellar syndrome; and autonomic dysfunction.
- [0320] In some embodiments, symptoms of the poorly levodopa-responsive parkinsonism are bradykinesia with rigidity, tremor, and/or postural instability. In some embodiments, symptoms of cerebellar syndrome are gait ataxia with cerebellar dysarthria, limb ataxia, and/or cerebellar oculomotor dysfunction. In some embodiments, the symptoms of parkinsonism are bradykinesia with rigidity tremor and/or postural instability.
- [0321] In some embodiments, the RBD subject is not diagnosed with one or more core clinical features, syndromes, or symptoms associated with the prodromal phase of MSA.
- [0322] In some embodiments, the RBD subject is diagnosed with one or more core clinical features, syndromes, or symptoms associated with the prodromal phase of MSA. In some embodiments, the core clinical features, syndromes, or symptoms associated with the prodromal phase of MSA are RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and/or urogenital failure. In some embodiments, the RBD subject is diagnosed with one or more of RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and/or urogenital failure. In some embodiments, the RBD subject is diagnosed with two or more of RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and/or urogenital failure. In some embodiments, the RBD subject is diagnosed with RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and urogenital failure.
- [0323] In some embodiments, administration of the N-acetyl-leucine reduces the number of RBD episodes as compared to the number of RBD episodes prior to administration of the N-acetyl-leucine.

- [0324] In some embodiments, administration of the N-acetyl-leucine reduces the RBD subject's RBD daily severity score as compared to the RBD subject's RBD daily severity score prior to administration of the N-acetyl-leucine.
- [0325] In some embodiments, administration of the N-acetyl-leucine reduces the frequency of RBD behaviors compared to prior to administration of the N-acetyl-leucine. In some embodiments, the RBD behaviors are selected from the group consisting of vocalizations, simple and complex motor behaviors, and any combination thereof. In some embodiments, administration of the N-acetyl-leucine reduces the severity of RBD behaviors compared to prior to administration of the N-acetyl-leucine.
- [0326] In some embodiments, administration of the N-acetyl-leucine decreases the number of nights with injurious behaviors to RBD subject or bed partner per week compared to prior to administration of the N-acetyl-leucine. In some embodiments, the injurious behaviors are selected from a group consisting of vocalizations, simple and complex motor behaviors, and any combination thereof.
- [0327] In some embodiments, administration of the N-acetyl-leucine decreases the number of nightmares per week compared to prior to administration of the N-acetyl-leucine.
- [0328] In some embodiments, the RBD subject is administered about 0.01 g to about 100 g of N-acetyl-leucine per day. In some embodiments, the RBD subject is administered about 0.1 g to about 20 g, about 0.5 g to about 15 g, about 1 g to about 15 g, about 1 g to about 10 g, or about 1 g to about 5 g of the N-acetyl-leucine per day. In some embodiments, the RBD subject is administered about 5 g of the N-acetyl-leucine per day.
- [0329] In some embodiments, the N-acetyl-leucine is administered orally.
- [0330] In some embodiments, the RBD subject is administered N-acetyl-DL-leucine. In some embodiments, the RBD subject is administered N-acetyl-L-leucine.

IV. N-Acetyl-Leucine

- [0331] The N-acetyl-leucine, or a pharmaceutically acceptable salt of the same, may be formulated and administered to a subject in accordance with known teachings in the art. For example, the N-acetyl-leucine, or a pharmaceutically acceptable salt of the same, may be formulated as a pharmaceutical composition. The pharmaceutical composition may comprise N-acetyl-leucine, or a pharmaceutically acceptable salt of the same, and a

pharmaceutically acceptable carrier. Reference to the pharmaceutical composition encompasses the active agent alone or in the form of a pharmaceutical composition.

[0332] The pharmaceutical composition may take any of a number of different forms depending, in particular, on the manner in which it is to be used. Thus, for example, it may be in the form of a powder, tablet, capsule, liquid, ointment, cream, gel, hydrogel, aerosol, spray, micellar solution, transdermal patch, liposome suspension or any other suitable form that may be administered to a person or animal in need of treatment.

[0333] In one embodiment, the pharmaceutically acceptable carrier may be a solid, and the composition may be in the form of a powder or tablet. A solid pharmaceutically acceptable carrier may include, but is not limited to, one or more substances which may also act as flavouring agents, buffers, lubricants, stabilisers, solubilisers, suspending agents, wetting agents, emulsifiers, dyes, fillers, glidants, compression aids, inert binders, sweeteners, preservatives, dyes, coatings, or tablet-disintegrating agents. The carrier may also be an encapsulating material. In powders, the carrier may be a finely divided solid that is in admixture with the finely divided active agents according to the disclosure. In tablets, the active agent may be mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets may, for example, contain up to 99% of the active agents. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins. In another embodiment, the pharmaceutically acceptable carrier may be a gel and the composition may be in the form of a cream or the like.

[0334] The carrier may include, but is not limited to, one or more excipients or diluents. Examples of such excipients are gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like.

[0335] In another embodiment, the pharmaceutically acceptable carrier may be a liquid. In one embodiment, the pharmaceutical composition is in the form of a solution. Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The N-acetyl-leucine may be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier may contain other

suitable pharmaceutical additives such as solubilisers, emulsifiers, buffers, preservatives, sweeteners, flavouring agents, suspending agents, thickening agents, colours, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, such as sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier may also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurised compositions may be a halogenated hydrocarbon or other pharmaceutically acceptable propellant.

[0336] Liquid pharmaceutical compositions, which are sterile solutions or suspensions, may be utilised by, for example, intramuscular, intrathecal, epidural, intraperitoneal, intravenous and particularly subcutaneous injection. The active agent may be prepared as a sterile solid composition that may be dissolved or suspended at the time of administration using sterile water, saline, or other appropriate sterile injectable medium.

[0337] The compositions may be administered orally in the form of a sterile solution or suspension containing other solutes or suspending agents (for example, enough saline or glucose to make the solution isotonic), bile salts, acacia, gelatin, sorbitan monoleate, polysorbate 80 (oleate esters of sorbitol and its anhydrides copolymerized with ethylene oxide) and the like. The compositions may also be administered orally either in liquid or solid composition form. Compositions suitable for oral administration include solid forms, such as pills, capsules, granules, tablets, and powders, and liquid forms, such as solutions, syrups, elixirs, and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions, and suspensions.

[0338] N-Acetyl-leucine and compositions comprising the same may alternatively be administered by inhalation (e.g. intranasally). Compositions may also be formulated for topical use. For instance, creams or ointments may be applied to the skin.

[0339] N-Acetyl-leucine may be incorporated within a slow or delayed-release device. Such devices may, for example, be inserted on or under the skin, and the medicament may be released over weeks or even months. Such devices may be advantageous when long-term treatment with N-acetyl-leucine used according to the present disclosure is required

and which would normally require frequent administration (e.g. at least daily administration).

- [0340] In one embodiment, the pharmaceutical composition is in the form of a tablet. In tablets, the active agent may be mixed with a vehicle, such as a pharmaceutically acceptable carrier, having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The tablets may contain up to 99% by weight of the active agents.
- [0341] For example, the N-acetyl-leucine, or a pharmaceutically acceptable salt of the same, may be provided in a solid dosage form suitable for oral administration, notably in the form of a tablet.
- [0342] Pharmaceutical compositions in solid oral dosage form, such as tablets, may be prepared by any method known in the art of pharmacy. Pharmaceutical compositions are usually prepared by mixing the N-acetyl-leucine, or a pharmaceutically acceptable salt thereof, with conventional pharmaceutically acceptable carriers.
- [0343] A tablet may be formulated as is known in the art. Tanganil®, for example, includes wheat starch, pregelatinised maize (corn) starch, calcium carbonate and magnesium stearate as excipients. The same, or similar, excipients, for example, may be employed with the present disclosure.

V. Particular Embodiments

- [0344] The present disclosure provides the following particular embodiments.
- [0345] Embodiment 1. A method of treating the prodromal phase of an alpha-synucleinopathy in a subject in need thereof, the method comprising administering a therapeutically effective amount of N acetyl-leucine to the subject, wherein the subject:
- [0346] (i) is not diagnosed with any of the core clinical features, syndromes, or symptoms associated with the alpha synucleinopathy; and
- [0347] (ii) is diagnosed with one or more core clinical features, syndromes, or symptoms associated with the prodromal phase of the alpha synucleinopathy,
- [0348] wherein the alpha-synucleinopathy is Parkinson's disease (PD), dementia with Lewy bodies (DLB), or multiple systems atrophy (MSA).
- [0349] Embodiment 2. The method of Embodiment 1 for treating the prodromal phase of PD in a subject in need thereof, wherein the subject:

- [0350] (i) is not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and
- [0351] (ii) is diagnosed with one or more of hyposmia, cognitive impairment, REM-sleep behavior disorder (RBD), constipation, depression, and/or anxiety.
- [0352] Embodiment 3. The method of Embodiment 1 for treating the prodromal phase of DLB in a subject in need thereof, wherein the subject:
- [0353] (i) is not diagnosed with dementia; and
- [0354] (ii) is diagnosed with one or more of RBD, constipation, hyposmia, depression, and/or orthostatic hypotension/dizziness.
- [0355] Embodiment 4. The method of Embodiment 1 for treating the prodromal phase of MSA in a subject in need thereof, wherein the subject:
- [0356] (i) is not diagnosed with (a) an autonomic dysfunction; and (b) poorly L-dopa-responsive parkinsonism and/or cerebellar syndrome; and
- [0357] (ii) is diagnosed with one or more of RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and/or urogenital failure.
- [0358] Embodiment 5. The method of any one of Embodiments 1-4, wherein the subject has decreased dopaminergic function in the basal ganglia.
- [0359] Embodiment 6. The method of any one of Embodiments 1-5, wherein administering the N-acetyl-leucine increases the dopaminergic function in the subject as compared to prior to administration of the N-acetyl-leucine.
- [0360] Embodiment 7. The method of Embodiments 5 or 6, wherein the amount dopaminergic function in the subject is determined by a dopamine transporter (DAT) scan.
- [0361] Embodiment 8. The method of any one of Embodiments 1-7, wherein the subject has decreased glucose metabolism in the brain.
- [0362] Embodiment 9. The method of any one of Embodiments 1-8, wherein the subject has decreased glucose metabolism in the parietal, occipital, and/or frontal regions of the brain.
- [0363] Embodiment 10. The method of any one of Embodiments 1-8, wherein the subject has decreased glucose metabolism in the occipital association cortex and primary visual area of the brain.

- [0364] Embodiment 11. The method of any one of Embodiments 1-8, wherein the subject has decreased glucose metabolism in the putamen nuclei, anterior cerebellar hemispheres, and/or the vermis.
- [0365] Embodiment 12. The method of any one of Embodiments 1-11, wherein administering the N-acetyl-leucine increases the glucose metabolism in the brain of the subject as compared to the glucose metabolism in the subject prior to administration of the N-acetyl-leucine.
- [0366] Embodiment 13. The method of any one of Embodiments 1-12, and wherein administering the N-acetyl-leucine increases the glucose metabolism in the parietal, occipital, and/or frontal regions of the brain of the subject as compared to the glucose metabolism in the subject prior to administration of the N-acetyl-leucine.
- [0367] Embodiment 14. The method of any one of Embodiments 1-12, and wherein administering the N-acetyl-leucine increases the glucose metabolism in the occipital association cortex and primary visual area of the brain of the subject as compared to the glucose metabolism in the subject prior to administration of the N-acetyl-leucine.
- [0368] Embodiment 15. The method of any one of Embodiments 1-12, and wherein administering the N-acetyl-leucine increases the glucose metabolism in the putamen nuclei, anterior cerebellar hemispheres, and/or the vermis of the subject as compared to the glucose metabolism in the subject prior to administration of the N-acetyl-leucine.
- [0369] Embodiment 16. The method of any one of Embodiments 8-15, wherein the glucose metabolism is determined by a positron emission tomography (PET) scan.
- [0370] Embodiment 17. The method of Embodiment 16, wherein the PET scan is a fluorodeoxyglucose-positron emission tomography (FDG-PET) scan.
- [0371] Embodiment 18. The method of Embodiment 17, wherein the FDG-PET scan is used to generate the subject's z-score.
- [0372] Embodiment 19. The method of Embodiment 18, wherein administering the N-acetyl-leucine reduces the subject's z-score in the parietal, occipital, and/or frontal regions of the brain.
- [0373] Embodiment 20. The method of Embodiment 18, wherein administering the N-acetyl-leucine reduces the subject's z-score in the frontal, parietal, and/or occipital regions of the brain.

- [0374] Embodiment 21. The method of Embodiment 18, wherein administering the N-acetyl-leucine reduces the subject's z-score in the putamen nuclei, anterior cerebellar hemispheres, and/or the vermis.
- [0375] Embodiment 22. The method of any one of Embodiments 18-21, wherein the subject's z-score is reduced by at least about 5%, about 10%, about 20%, about 30%, about 40%, or about least 50% compared to the subject's z-score prior to administration of the N-acetyl-leucine.
- [0376] Embodiment 23. The method of any one of Embodiments 1-22, wherein administration of the N-acetyl-leucine reduces the number of RBD episodes as compared to the number of RBD episodes prior to administration of the N-acetyl-leucine.
- [0377] Embodiment 24. A method of treating REM-sleep behavior disorder (RBD) in a subject in need thereof, the method comprising administering a therapeutically effective amount of N-acetyl-leucine to the subject.
- [0378] Embodiment 25. The method of Embodiment 24, wherein the subject has been diagnosed with prodromal Parkinson's disease (PD); prodromal dementia with Lewy bodies (DLB); or prodromal multiple systems atrophy (MSA).
- [0379] Embodiment 26. The method of Embodiment 24, wherein the subject has been diagnosed with classical Parkinson's disease (PD), classical dementia with Lewy bodies (DLB), or classical multiple systems atrophy (MSA).
- [0380] Embodiment 27. The method of any one of Embodiments 1-26, wherein about 1 g to about 15 g of the N acetyl-leucine is administered to the subject per day.
- [0381] Embodiment 28. The method of Embodiment 27, wherein about 1 g to about 10 g of the N-acetyl-leucine is administered to the subject per day.
- [0382] Embodiment 29. The method of Embodiment 28, wherein about 1 g to about 5 g of the N-acetyl-leucine is administered to the subject per day.
- [0383] Embodiment 30. The method of any one of Embodiments 1-29, wherein the N-acetyl-leucine is administered orally to the subject.
- [0384] Embodiment 31. The method of any one of Embodiments 1-30, wherein the N-acetyl-leucine administered to the subject is N-acetyl-DL-leucine.
- [0385] Embodiment 32. The method of any one of Embodiments 1-30, wherein the N-acetyl-leucine administered to the subject is N-acetyl-L-leucine.

- [0386] Embodiment 33. N-Acetyl-leucine for use in treating the prodromal phase of an alpha-synucleinopathy in a subject in need thereof, wherein the subject:
- [0387] (i) is not diagnosed with any of the core clinical features, syndromes, or symptoms associated with the alpha synucleinopathy; and
- [0388] (ii) is diagnosed with one or more core clinical features, syndromes, or symptoms associated with the prodromal phase of the alpha synucleinopathy,
- [0389] wherein the alpha-synucleinopathy is Parkinson's disease (PD), dementia with Lewy bodies (DLB), or multiple systems atrophy (MSA).
- [0390] Embodiment 34. The N-acetyl-leucine of Embodiment 33 for use in treating the prodromal phase of PD in a subject in need thereof, wherein the subject:
- [0391] (i) is not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and
- [0392] (ii) is diagnosed with one or more of hyposmia, cognitive impairment, REM-sleep behavior disorder (RBD), constipation, depression, and/or anxiety.
- [0393] Embodiment 35. The N-acetyl-leucine of Embodiment 33 for use in treating the prodromal phase of DLB in a subject in need thereof, wherein the subject:
- [0394] (i) is not diagnosed with dementia; and
- [0395] (ii) is diagnosed with one or more of RBD, constipation, hyposmia, depression, and/or orthostatic hypotension/dizziness.
- [0396] Embodiment 36. The N-acetyl-leucine of Embodiment 33 for use in treating the prodromal phase of MSA in a subject in need thereof, wherein the subject:
- [0397] (i) is not diagnosed with (a) an autonomic dysfunction; and (b) poorly L-dopa-responsive parkinsonism and/or cerebellar syndrome; and
- [0398] (ii) is diagnosed with one or more of RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and/or urogenital failure.
- [0399] Embodiment 37. The N-acetyl-leucine for use of any one of Embodiments 33-36, wherein the subject has decreased dopaminergic function in the basal ganglia.
- [0400] Embodiment 38. The N-acetyl-leucine for use of any one of Embodiments 33-37, wherein administering the N-acetyl-leucine increases the dopaminergic function in the subject as compared to prior to administration of the N-acetyl-leucine.

- [0401] Embodiment 39. The N-acetyl-leucine for use of Embodiments 37 or 39, wherein the amount dopaminergic function in the subject is determined by a dopamine transporter (DAT) scan.
- [0402] Embodiment 40. The N-acetyl-leucine for use of any one of Embodiments 33-39, wherein the subject has decreased glucose metabolism in the brain.
- [0403] Embodiment 41. The N-acetyl-leucine for use of any one of Embodiments 33-40, wherein the subject has decreased glucose metabolism in the parietal, occipital, and/or frontal regions of the brain.
- [0404] Embodiment 42. The N-acetyl-leucine for use of any one of Embodiments 33-40, wherein the subject has decreased glucose metabolism in the occipital association cortex and primary visual area of the brain.
- [0405] Embodiment 43. The N-acetyl-leucine for use of any one of Embodiments 33-40, wherein the subject has decreased glucose metabolism in the putamen nuclei, anterior cerebellar hemispheres, and/or the vermis.
- [0406] Embodiment 44. The N-acetyl-leucine for use of any one of Embodiments 33-43, wherein administering the N-acetyl-leucine increases the glucose metabolism in the brain of the subject as compared to the glucose metabolism in the subject prior to administration of the N-acetyl-leucine.
- [0407] Embodiment 45. The N-acetyl-leucine for use of any one of Embodiments 33-44, and wherein administering the N-acetyl-leucine increases the glucose metabolism in the parietal, occipital, and/or frontal regions of the brain of the subject as compared to the glucose metabolism in the subject prior to administration of the N-acetyl-leucine.
- [0408] Embodiment 46. The N-acetyl-leucine for use of any one of Embodiments 33-44, and wherein administering the N-acetyl-leucine increases the glucose metabolism in the occipital association cortex and primary visual area of the brain of the subject as compared to the glucose metabolism in the subject prior to administration of the N-acetyl-leucine.
- [0409] Embodiment 47. The N-acetyl-leucine for use of any one of Embodiments 33-44, and wherein administering the N-acetyl-leucine increases the glucose metabolism in the putamen nuclei, anterior cerebellar hemispheres, and/or the vermis of the subject as compared to the glucose metabolism in the subject prior to administration of the N-acetyl-leucine.

- [0410] Embodiment 48. The N-acetyl-leucine for use of any one of Embodiments 40-47, wherein the glucose metabolism is determined by a positron emission tomography (PET) scan.
- [0411] Embodiment 49. The N-acetyl-leucine for use of Embodiment 48, wherein the PET scan is a fluorodeoxyglucose-positron emission tomography (FDG-PET) scan.
- [0412] Embodiment 50. The N-acetyl-leucine for use of Embodiment 49, wherein the FDG-PET scan is used to generate the subject's z-score.
- [0413] Embodiment 51. The N-acetyl-leucine for use of Embodiment 50, wherein administering the N-acetyl-leucine reduces the subject's z-score in the parietal, occipital, and/or frontal regions of the brain.
- [0414] Embodiment 52. The N-acetyl-leucine for use of Embodiment 50, wherein administering the N-acetyl-leucine reduces the subject's z-score in the frontal, parietal, and/or occipital regions of the brain.
- [0415] Embodiment 53. The N-acetyl-leucine for use of Embodiment 50, wherein administering the N-acetyl-leucine reduces the subject's z-score in the putamen nuclei, anterior cerebellar hemispheres, and/or the vermis.
- [0416] Embodiment 54. The N-acetyl-leucine for use of any one of Embodiments 50-53, wherein the subject's z-score is reduced by at least about 5%, about 10%, about 20%, about 30%, about 40%, or about least 50% compared to the subject's z-score prior to administration of the N-acetyl-leucine.
- [0417] Embodiment 55. The N-acetyl-leucine for use of any one of Embodiments 33-54, wherein administration of the N-acetyl-leucine reduces the number of RBD episodes as compared to the number of RBD episodes prior to administration of the N-acetyl-leucine.
- [0418] Embodiment 56. N-Acetyl-leucine for use in treating REM-sleep behavior disorder (RBD) in a subject in need thereof.
- [0419] Embodiment 57. The N-acetyl-leucine for use of Embodiment 56, wherein the subject has been diagnosed with prodromal Parkinson's disease (PD); prodromal dementia with Lewy bodies (DLB); or prodromal multiple systems atrophy (MSA).
- [0420] Embodiment 58. The N-acetyl-leucine for use of Embodiment 56, wherein the subject has been diagnosed with classical Parkinson's disease (PD), classical dementia with Lewy bodies (DLB), or classical multiple systems atrophy (MSA).

- [0421] Embodiment 59. The N-acetyl-leucine for use of any one of Embodiments 33-58, wherein about 1 g to about 15 g of the N acetyl-leucine is administered to the subject per day.
- [0422] Embodiment 60. The N-acetyl-leucine for use of Embodiment 59, wherein about 1 g to about 10 g of the N-acetyl-leucine is administered to the subject per day.
- [0423] Embodiment 61. The N-acetyl-leucine for use of Embodiment 60, wherein about 1 g to about 5 g of the N-acetyl-leucine is administered to the subject per day.
- [0424] Embodiment 62. The N-acetyl-leucine for use of any one of Embodiments 33-61, wherein the N-acetyl-leucine is administered orally to the subject.
- [0425] Embodiment 63. The N-acetyl-leucine for use of any one of Embodiments 33-62, wherein the N-acetyl-leucine administered to the subject is N-acetyl-DL-leucine.
- [0426] Embodiment 64. The N-acetyl-leucine for use of any one of Embodiments 33-62, wherein the N-acetyl-leucine administered to the subject is N-acetyl-L-leucine.
- [0427] Embodiment 65. Use of N-Acetyl-leucine in the manufacture of a medicament for treating the prodromal phase of an alpha-synucleinopathy in a subject in need thereof, wherein the subject:
- [0428] (i) is not diagnosed with any of the core clinical features, syndromes, or symptoms associated with the alpha synucleinopathy; and
- [0429] (ii) is diagnosed with one or more core clinical features, syndromes, or symptoms associated with the prodromal phase of the alpha synucleinopathy,
- [0430] wherein the alpha-synucleinopathy is Parkinson's disease (PD), dementia with Lewy bodies (DLB), or multiple systems atrophy (MSA).
- [0431] Embodiment 66. The use of Embodiment 65 for use in treating the prodromal phase of PD in a subject in need thereof, wherein the subject:
- [0432] (i) is not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and
- [0433] (ii) is diagnosed with one or more of hyposmia, cognitive impairment, REM-sleep behavior disorder (RBD), constipation, depression, and/or anxiety.
- [0434] Embodiment 67. The Nuse of Embodiment 65 for use in treating the prodromal phase of DLB in a subject in need thereof, wherein the subject:

- [0435] (i) is not diagnosed with dementia; and
- [0436] (ii) is diagnosed with one or more of RBD, constipation, hyposmia, depression, and/or orthostatic hypotension/dizziness.
- [0437] Embodiment 68. The use of Embodiment 65 for use in treating the prodromal phase of MSA in a subject in need thereof, wherein the subject:
- [0438] (i) is not diagnosed with (a) an autonomic dysfunction; and (b) poorly L-dopa-responsive parkinsonism and/or cerebellar syndrome; and
- [0439] (ii) is diagnosed with one or more of RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and/or urogenital failure.
- [0440] Embodiment 69. The N use of any one of Embodiments 65-68, wherein the subject has decreased dopaminergic function in the basal ganglia.
- [0441] Embodiment 70. The N use of any one of Embodiments 65-69, wherein administering the N-acetyl-leucine increases the dopaminergic function in the subject as compared to prior to administration of the N-acetyl-leucine.
- [0442] Embodiment 71. The use of Embodiments 69 or 70, wherein the amount dopaminergic function in the subject is determined by a dopamine transporter (DAT) scan.
- [0443] Embodiment 72. The use of any one of Embodiments 65-71, wherein the subject has decreased glucose metabolism in the brain.
- [0444] Embodiment 73. The use of any one of Embodiments 65-72, wherein the subject has decreased glucose metabolism in the parietal, occipital, and/or frontal regions of the brain.
- [0445] Embodiment 74. The use of any one of Embodiments 65-72, wherein the subject has decreased glucose metabolism in the occipital association cortex and primary visual area of the brain.
- [0446] Embodiment 75. The use of any one of Embodiments 65-72, wherein the subject has decreased glucose metabolism in the putamen nuclei, anterior cerebellar hemispheres, and/or the vermis.
- [0447] Embodiment 76. The use of any one of Embodiments 65-75, wherein administering the N-acetyl-leucine increases the glucose metabolism in the brain of the subject as compared to the glucose metabolism in the subject prior to administration of the N-acetyl-leucine.

- [0448] Embodiment 77. The N use of any one of Embodiments 65-76, and wherein administering the N-acetyl-leucine increases the glucose metabolism in the parietal, occipital, and/or frontal regions of the brain of the subject as compared to the glucose metabolism in the subject prior to administration of the N-acetyl-leucine.
- [0449] Embodiment 78. The use of any one of Embodiments 65-76, and wherein administering the N-acetyl-leucine increases the glucose metabolism in the occipital association cortex and primary visual area of the brain of the subject as compared to the glucose metabolism in the subject prior to administration of the N-acetyl-leucine.
- [0450] Embodiment 79. The use of any one of Embodiments 65-76, and wherein administering the N-acetyl-leucine increases the glucose metabolism in the putamen nuclei, anterior cerebellar hemispheres, and/or the vermis of the subject as compared to the glucose metabolism in the subject prior to administration of the N-acetyl-leucine.
- [0451] Embodiment 80. The use of any one of Embodiments 72-79, wherein the glucose metabolism is determined by a positron emission tomography (PET) scan.
- [0452] Embodiment 81. The use of Embodiment 80, wherein the PET scan is a fluorodeoxyglucose-positron emission tomography (FDG-PET) scan.
- [0453] Embodiment 82. The use of Embodiment 80, wherein the FDG-PET scan is used to generate the subject's z-score.
- [0454] Embodiment 83. The use of Embodiment 82, wherein administering the N-acetyl-leucine reduces the subject's z-score in the parietal, occipital, and/or frontal regions of the brain.
- [0455] Embodiment 84. The use of Embodiment 82, wherein administering the N-acetyl-leucine reduces the subject's z-score in the frontal, parietal, and/or occipital regions of the brain.
- [0456] Embodiment 85. The N use of Embodiment 82, wherein administering the N-acetyl-leucine reduces the subject's z-score in the putamen nuclei, anterior cerebellar hemispheres, and/or the vermis.
- [0457] Embodiment 86. The use of any one of Embodiments 82-85, wherein the subject's z-score is reduced by at least about 5%, about 10%, about 20%, about 30%, about 40%, or about least 50% compared to the subject's z-score prior to administration of the N-acetyl-leucine.

- [0458] Embodiment 87. The use of any one of Embodiments 65-86, wherein administration of the N-acetyl-leucine reduces the number of RBD episodes as compared to the number of RBD episodes prior to administration of the N-acetyl-leucine.
- [0459] Embodiment 88. Use of N-acetyl-leucine in the manufacture of a medicament in treating REM-sleep behavior disorder (RBD) in a subject in need thereof.
- [0460] Embodiment 89. The use of Embodiment 88, wherein the subject has been diagnosed with prodromal Parkinson's disease (PD); prodromal dementia with Lewy bodies (DLB); or prodromal multiple systems atrophy (MSA).
- [0461] Embodiment 90. The use of Embodiment 88, wherein the subject has been diagnosed with classical Parkinson's disease (PD), classical dementia with Lewy bodies (DLB), or classical multiple systems atrophy (MSA).
- [0462] Embodiment 91. The use of any one of Embodiments 65-90, wherein about 1 g to about 15 g of the N acetyl-leucine is administered to the subject per day.
- [0463] Embodiment 92. The use of Embodiment 91, wherein about 1 g to about 10 g of the N-acetyl-leucine is administered to the subject per day.
- [0464] Embodiment 93. The use of Embodiment 92, wherein about 1 g to about 5 g of the N-acetyl-leucine is administered to the subject per day.
- [0465] Embodiment 94. The use of any one of Embodiments 65-95, wherein the N-acetyl-leucine is administered orally to the subject.
- [0466] Embodiment 95. The use of any one of Embodiments 65-94, wherein the N-acetyl-leucine administered to the subject is N-acetyl-DL-leucine.
- [0467] Embodiment 96. The use of any one of Embodiments 65-94, wherein the N-acetyl-leucine administered to the subject is N-acetyl-L-leucine.

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Examples

EXAMPLE 1

N-Acetyl-DL-Leucine Administration in Patients with Prodromal Parkinson's Disease

- [0521] Isolated REM-Sleep-Behavior-Disorder (iRBD) is a prodromal phenotype of Parkinson's Disease (PD) with an >85 % risk of conversion to PD or Lewy Body Dementia (LBD) within 10-15 years^{1,2}. Currently, there are no proven strategies for the treatment of iRBD or slowing the progression of PD. Two patients with iRBD who were

part of a long-term observational study with annual clinical monitoring and functional imaging were treated for more than 18 months with 5 g/day oral N- acetyl-DL-leucine (ADLL) and monitored. The patient's 3-weeks-RBD-severity-sumscore (RBD-SS-3), Dopamine-Transporter-Ligand-Binding-(DAT)-SPECT, and metabolic "Parkinson-Disease-related-Pattern (PDRP)"-z-score in Fluoro-Deoxy-Glucose-Positron-Emission-Tomography (FDG-PET) were measured annually. No adverse effects were reported in either patient with ADLL-treatment.

[0522] Patient 1 was a 74-year-old female reported symptoms of RBD starting in 2006. Video-polysomnography confirmed the diagnosis of iRBD in 2011. For symptomatic treatment of iRBD, she had been prescribed a daily dose of 0.5 mg clonazepam at night since 2018. She underwent 4 pretreatment DAT-SPECTs in 2013, 2014, 2016 and 2019. In November 2021, she began taking 5 g/dday ADLL, i.e. about three years after the last "baseline" DAT-SPECT in 2019 and after the second FDG-PET in 2018. After 3 months of ADLL treatment, she received the next DAT-SPECT in February 2022 and a further DAT-SPECT under continued ADLL therapy in September 2023. Likewise, after taking 13 months continuous ADLL therapy, she underwent a third (prescheduled) FDG-PET in December 2022.

[0523] Patient 2 was a 54-year-old male that reported RBD-symptoms in 2018. Video-polysomnography confirmed the diagnosis in June 2020. He did not take any symptomatic therapy for iRBD nor any other concomitant medication. He received a baseline DAT-SPECT in August 2020 and an FDG-PET in June 2020 19/17 months (respectively) before starting continuous ADLL-therapy (5 g/day) in January 2022. Twelve months later, he underwent a second (under ADLL therapy) FDG-PET in January 2023 and 18 months later a second (under ADLL therapy) DAT-SPECT in July 2023.

REM-Sleep Behavior Disorder (RBD)

[0524] Following the start of ADLL treatment, RBD-severity was evaluated daily by the patient and spouse in an RBD-diary (daily severity score with a range of 0-4, 4 indicating highest severity). For this study, daily scores were analyzed for a period of 561 days. Daily scores were summed up to a three-week score (RBD-SS-3). Patient 1 and Patient 2's RBD-SS-3 sumscores are shown in FIGs. 1A-1B.

- [0525] Patient 1 had a RBD-SS-3 score of 21 prior to treatment. Three weeks after starting ADLL-treatment, Patient 1's RBD-SS-3 score declined to 5 and aggressive dream content was nearly absent (FIG. 1A). This effect remained at this low level for the following 21 months. At baseline, olfactory function tests revealed anosmia with a TDI-sum score of 6. Regularly assessed UPDRS III (motor), MoCA and SCOPA-AUT scores were normal and did not change over >20-months treatment period.
- [0526] Patient 2 was less severely affected by RBD-symptoms than Patient 1. Three weeks after starting ADLL therapy, Patient 2's RBD-SS-3 score decreased from 7 to 0 (FIG. 1B). The aggressive content of his dreams disappeared entirely. Arrowheads indicate a recurrence of the RBD-phenotype under substantial intake of alcohol during two short holidays (weeks 7-9 and 10-12). The enhancement of RBD symptoms by alcohol intake is a known feature in RBD. Subsequently, the patient completely abstained from alcohol consumption for the remaining time of the study.
- [0527] These improvements were – apart from an occasional re-appearance of dream enactment – maintained for the next 18 months of ADLL treatment. Olfactory function tests revealed anosmia with a TDI-sum score of 10 at baseline. Regularly assessed UPDRS III (motor), MoCA and SCOPA-AUT scores were normal and remained normal during ADLL therapy.

Nigrostriatal Dopaminergic Denervation

- [0528] Serial presynaptic Dopamine Transporter (DAT) binding by ¹²³I-FP-CIT-SPECT-imaging (DAT-SPECT) was assessed to monitor the change (progression in time) of the nigrostriatal dopaminergic system. A lower striatal-to-occipital binding ratio on DAT-SPECT indicates a stronger loss of dopaminergic terminals due to neurodegeneration.
- [0529] In the right putamen of Patient 1, the pretreatment DAT-ligand-binding-ratio value was 1.88 (normal) in 02/2013, decreased to 1.63 in 03/2014 and then decreased further to 1.22 in 01/2019 (FIG. 2A). These data indicate that there was a progressive neurodegeneration of the nigrostriatal dopaminergic projection over 5 years – a hallmark of late prodromal and early PD. In 02/2022, three months after initiation of ADLL treatment, the patient's right putamen DAT-SPECT score was slightly increased to 1.43. After 22 months of ADLL therapy, the score further increased to 1.67. Thus, oral ADLL therapy partially reversed the decline of the DAT-SPECT score, almost normalizing it

after just under 2 years of treatment. DAT-SPECT scores for Patient 1 are detailed in Table 7.

Table 7
Patient 1 DAT-SPECT scores

Right Caudate	Left Caudate	Right Putamen	Left Putamen	Right Striatum	Left Striatum
Feb. 2013					
1.99	1.80	1.88	1.85	1.94	1.82
Mar. 2014					
2.02	1.85	1.63	1.79	1.84	1.82
Apr. 2016					
1.61	1.36	1.27	1.42	1.45	1.39
Jan. 2019					
1.44	1.17	1.22	1.31	1.34	1.24
3 months after start of treatment (Feb. 2022)					
1.70	1.28	1.43	1.29	1.57	1.29
22 months after start of treatment (Sept. 2023)					
1.97	2.09	1.67	1.68	1.83	1.90

[0530] The imaging biomarkers of Patient 2 also showed the same pattern of change with ADLL treatment as in Patient 1. Patient 2's striatal-occipital ligand binding ratios of the DAT-SPECT images are presented in FIG. 2B. The patient's pretreatment right putamen DAT-SPECT score was 1.42 in 08/2020. After 17 months of ADLL treatment, the score increased to 1.72 – nearly back to normal values. DAT-SPECT scores for right caudate, left caudate, right putamen, left putamen, right striatum, and left striatum are detailed in Table 8. The patient's DAT-SPECT scores continued to increase through 30-months after initiation of treatment.

Table 8
Patient 2 DAT-SPECT scores

Right Caudate	Left Caudate	Right Putamen	Left Putamen	Right Striatum	Left Striatum
Baseline (Aug. 2020)					
1.65	1.35	1.42	1.56	1.54	1.45
17 months after start of treatment (Jul. 2023)					
1.87	1.80	1.72	1.75	1.80	1.78
30 months after start of treatment (Aug. 2024)					

2.26	2.54	2.26	2.47	2.32	2.51
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Glucose Metabolism

- [0531] Serial ¹⁸Fluoro-Deoxyglucose PET-imaging (FDG-PET) was assessed to identify the pathologic metabolic “Parkinson disease related pattern (PDRP)” over time. Expression-z-scores for the PDRP were quantified in all scans (higher z-score value indicating stronger expression of PDRP). PDRP-z-scores were previously shown to increase with disease progression in iRBD and in PD and to decrease with effective (symptomatic) treatment.
- [0532] The two groups of untreated iRBD patients (converters and non-converters) show a steady increase in the expression of PDRP over an eight-year period. In Patient 1, the FDG-PET-z-score of the metabolic PDRP was 1.72 in 2014, rising to 3.28 in 2018, indicative of an impairment in brain metabolism (FIG. 3A). In 12/2022, 1 year after starting ADLL therapy, Patient 1's FDG-PET PDRP-z-score was 3.18 - similar to the z-score in 2018. In June 2020, Patient 2's pretreatment PDRP z-score was 1.02 (FIG. 3B). When the second FDG-PET was performed in 01/2023, after one-year of ADLL treatment, the z-score was 0.30.
- [0533] For comparison, in 13 other iRBD patients who did not receive treatment with ADLL (converters and non-converters) and whom had similarly timed FDG-PET scans, PDRP-z-scores continued to increase over the 8-year period indicating disease progression. Five of these 13 iRBD had converted to PD (converters), 1 to LBD, and 8 did not convert to PD (non-converters) in the 8-year-follow-up. Thus, ADLL treatment appeared to have stabilized or improved the metabolic activity in PD-related brain areas.
- [0534] The DAT-SPECT and FDG-PET data suggest that ADLL treatment might be modifying the progression to the PD phenotype. Striatal DAT-SPECT measures the abundance of the plasma membrane dopamine transporter (DAT) found in the axon terminals of substantia nigra dopaminergic neurons. Loss of these axons has long been linked to the emergences of PD symptoms (Marek, K. Et al. *Ann Clin Transl Neurol.* 5(12):1460-1477 (2018)). In animal models of PD, there is a down-regulation in axonal DAT expression prior to frank neurodegeneration (González-Rodríguez, P. et al. *Nature.* 599(7886):650-656 (2021)). Similarly, FDG-PET-based measurements of PDRP-z-score suggest that ADLL-treatment halted the progressive network dysfunction triggered by the

loss of dopaminergic axons. This conclusion was supported by the longitudinal comparison of FDG-PET PDRP z-scores in the 2 ADLL-treated versus the 13 untreated iRBD patients.

Cardiac Sympathetic Innervation

- [0535] [^{123}I]-Metaiodobenzylguanidine cardiac scintigraphy (MIBG) was performed to identify the effect of ADLL on cardiac sympathetic innervation in Patient 1 and 9 disease control iRBD participants at baseline according to standard operating procedures, which is detailed below. Patient 2 received MIBG investigation in May 2022. Regions of interest (ROI) were manually placed on planar anterior images, with a rectangular ROI for the mediastinum and a circular ROI for the left ventricle of the heart.
- [0536] For the MIBG testing, after blocking the thyroid gland with sodium perchlorate, 185 MBq 123I-FP-CIT (GE Healthcare) was administered to the patient intravenously. Scans were acquired on a dual-headed gamma camera (Symbia S; Siemens, Erlangen, Germany) exactly 180 minutes after injection. The images were obtained in 120 projections over a 360° arc with the step-and-shoot mode (40 seconds per projection). The quality of the DAT-SPECT procedure was independently and repeatedly controlled by the imaging group of the Parkinson's Progression Marker's Initiative study of the Michael J Fox Foundation, New York USA
- [0537] Both patients demonstrated a reduced cardiac sympathetic innervation, demonstrated by [^{123}I]-MIBG. In particular, in May 2014, Patient 1 had a heart-to-mediastinum ratio of [^{123}I]-MIBG-binding of 1.32. In May 2022, Patient 2 had a heart-to-mediastinum ratio of [^{123}I]-MIBG-binding of 0.98. A heart-to-mediastinum ratio of [^{123}I]-MIBG-binding of < 1.5 was considered pathological.
- [0538] Together, these data show the beneficial effects of a daily oral administration of ADLL were reflected in three outcome measures: 1) a marked decline in the subjectively assessed clinical severity of the RBD phenotype (disappearance of aggressive dream content, reduction of dream enactment); 2) a stabilization or reversal of the slow, progressive decline of striato-occipital binding ratios in DAT-SPECT; and 3) a stabilization or reversal in the progressive metabolic impairment in the PD-Related Pattern captured with FDG-PET.

EXAMPLE 2

N-Acetyl-DL-Leucine Administration in a Patient with RBD

- [0539] A 64-year old female patient with balance problems reported having symptoms of typical REM sleep behaviour disorder. Those symptoms were reported have occurred about four times a week with moderate severity.
- [0540] The patient was administered acetyl-leucine (4 grams) prior to going to bed. After administration of acetyl-leucine for four weeks, the patient reported a decrease in the frequency of REM sleep behaviour disorder symptoms, with less severe symptoms occurring only once per week. After three months of treatment, the patient reported that there was a slight improvement with even fewer symptoms. The patient has continued with treatment for five months.
- [0541] All of the features described herein (including any accompanying claims, abstract and drawings), and/or all of the steps of any method so disclosed, may be combined with any of the above aspects in any combination, except combinations where at least some of such features and/or steps are mutually exclusive.
- [0542] It is to be understood that the foregoing embodiments and exemplifications are not intended to be limiting in any respect to the scope of the disclosure, and that the claims presented herein are intended to encompass all embodiments and exemplifications whether or not explicitly presented herein.
- [0543] All patents, patent applications, and publications cited herein are fully incorporated by reference in their entirety

WHAT IS CLAIMED IS:

1. A method of treating the prodromal phase of an alpha-synucleinopathy in a subject in need thereof, the method comprising administering a therapeutically effective amount of N-acetyl-leucine to the subject, wherein the subject:
 - (i) is not diagnosed with any of the core clinical features, syndromes, or symptoms associated with the alpha-synucleinopathy; and
 - (ii) is diagnosed with one or more core clinical features, syndromes, or symptoms associated with the prodromal phase of the alpha-synucleinopathy, wherein the alpha-synucleinopathy is Parkinson's disease (PD), dementia with Lewy bodies (DLB), or multiple systems atrophy (MSA).
2. The method of claim 1 for treating the prodromal phase of PD in a subject in need thereof, wherein the subject:
 - (i) is not diagnosed with tremor, bradykinesia, muscle stiffness, impaired balance, and/or impaired coordination; and
 - (ii) is diagnosed with one or more of hyposmia, cognitive impairment, REM-sleep behavior disorder (RBD), constipation, depression, and/or anxiety.
3. The method of claim 1 for treating the prodromal phase of DLB in a subject in need thereof, wherein the subject:
 - (i) is not diagnosed with dementia; and
 - (ii) is diagnosed with one or more of RBD, constipation, hyposmia, depression, and/or orthostatic hypotension/dizziness.
4. The method of claim 1 for treating the prodromal phase of MSA in a subject in need thereof, wherein the subject:
 - (i) is not diagnosed with (a) an autonomic dysfunction; and (b) poorly L-dopa-responsive parkinsonism and/or cerebellar syndrome; and
 - (ii) is diagnosed with one or more of RBD, neurogenic orthostatic hypotension within 10 minutes of standing or head-up tilt, and/or urogenital failure.

5. The method of any one of claims 1-4, wherein the subject has decreased dopaminergic function in the basal ganglia.
6. The method of any one of claims 1-5, wherein administering the N-acetyl-leucine increases the dopaminergic function in the subject as compared to prior to administration of the N-acetyl-leucine.
7. The method of claims 5 or 6, wherein the amount of dopaminergic function in the subject is determined by a dopamine transporter (DAT) scan.
8. The method of any one of claims 1-7, wherein the subject has decreased glucose metabolism in the brain.
9. The method of any one of claims 1-8, wherein the subject has decreased glucose metabolism in the parietal, occipital, and/or frontal regions of the brain.
10. The method of any one of claims 1-8, wherein the subject has decreased glucose metabolism in the occipital association cortex and primary visual area of the brain.
11. The method of any one of claims 1-8, wherein the subject has decreased glucose metabolism in the putamen nuclei, anterior cerebellar hemispheres, and/or the vermis.
12. The method of any one of claims 1-11, wherein administering the N-acetyl-leucine increases the glucose metabolism in the brain of the subject as compared to the glucose metabolism in the subject prior to administration of the N-acetyl-leucine.
13. The method of any one of claims 1-12, wherein administering the N-acetyl-leucine increases the glucose metabolism in the parietal, occipital, and/or frontal regions of the brain of the subject as compared to the glucose metabolism in the subject prior to administration of the N-acetyl-leucine.

14. The method of any one of claims 1-12, wherein administering the N-acetyl-leucine increases the glucose metabolism in the occipital association cortex and primary visual area of the brain of the subject as compared to the glucose metabolism in the subject prior to administration of the N-acetyl-leucine.
15. The method of any one of claims 1-12, wherein administering the N-acetyl-leucine increases the glucose metabolism in the putamen nuclei, anterior cerebellar hemispheres, and/or the vermis of the subject as compared to the glucose metabolism in the subject prior to administration of the N-acetyl-leucine.
16. The method of any one of claims 8-15, wherein the glucose metabolism is determined by a positron emission tomography (PET) scan.
17. The method of claim 16, wherein the PET scan is a fluorodeoxyglucose-positron emission tomography (FDG-PET) scan.
18. The method of claim 17, wherein the FDG-PET scan is used to generate the subject's z-score.
19. The method of claim 18, wherein administering the N-acetyl-leucine reduces the subject's z-score in the parietal, occipital, and/or frontal regions of the brain.
20. The method of claim 18, wherein administering the N-acetyl-leucine reduces the subject's z-score in the medial occipital lobes, lateral occipital lobes, occipital association cortex, and/or primary visual area of the brain.
21. The method of claim 18, wherein administering the N-acetyl-leucine reduces the subject's z-score in the putamen nuclei, anterior cerebellar hemispheres, and/or the vermis.

22. The method of any one of claims 18-21, wherein the subject's z-score is reduced by at least about 5%, about 10%, about 20%, about 30%, about 40%, or about least 50% compared to the subject's z-score prior to administration of the N-acetyl-leucine.
23. The method of any one of claims 1-22, wherein administration of the N-acetyl-leucine reduces the number of RBD episodes as compared to the number of RBD episodes prior to administration of the N-acetyl-leucine.
24. The method of any one of claims 1-23, wherein the subject is diagnosed with hyposmia.
25. The method of claim 24, wherein hyposmia is diagnosed with one or more of a 12-item Brief Smell Identification Test (B-SIT) and sniffin sticks test (SST).
26. A method of treating REM-sleep behavior disorder (RBD) in a subject in need thereof, the method comprising administering a therapeutically effective amount of N-acetyl-leucine to the subject.
27. The method of claim 26, wherein the subject has been diagnosed with prodromal Parkinson's disease (PD), prodromal dementia with Lewy bodies (DLB), or prodromal multiple systems atrophy (MSA).
28. The method of claim 26, wherein the subject has not been diagnosed with classical Parkinson's disease (PD), classical dementia with Lewy bodies (DLB), or classical multiple systems atrophy (MSA).
29. The method of any one of claims 1-28, wherein about 1 g to about 15 g of the N-acetyl-leucine is administered to the subject per day.
30. The method of claim 29, wherein about 1 g to about 10 g of the N-acetyl-leucine is administered to the subject per day.

31. The method of claim 30, wherein about 1 g to about 5 g of the N-acetyl-leucine is administered to the subject per day.
32. The method of any one of claims 1-31, wherein the N-acetyl-leucine is administered orally to the subject.
33. The method of any one of claims 1-32, wherein the N-acetyl-leucine administered to the subject is N-acetyl-DL-leucine.
34. The method of any one of claims 1-32, wherein the N-acetyl-leucine administered to the subject is N-acetyl-L-leucine.