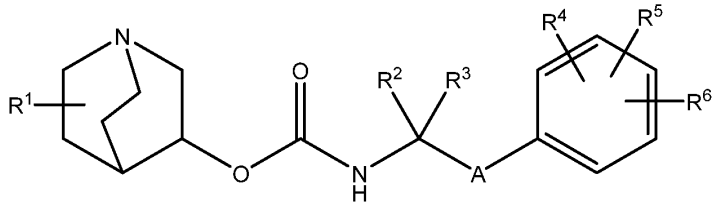
CLAIMS

What is Claimed:

1. A method for enhancing neuronal connectivity within the brain of a subject, such as in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of formula (I),



(I)

or a pharmaceutically acceptable salt or prodrug thereof, wherein:

R^1 is selected from hydrogen, halogen (e.g., fluorine), cyano, nitro, hydroxy, thio, amino, C_{1-6}-alkyl (e.g., methyl or ethyl), C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-alkyloxy, C_{2-6}-alkenyloxy, and C_{2-6}-alkynyloxy, wherein said alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, or alkynyloxy is optionally substituted with one or more (e.g., 1, 2, or 3) groups selected from halogen, cyano, nitro, hydroxy, thio, and amino;

R^2 and R^3 are independently selected from C_{1-3}-alkyl, optionally substituted by one or more (e.g., 1, 2, or 3) halogens, or R^2 and R^3 together form a cyclopropyl or cyclobutyl group, optionally substituted by one or more (e.g., 1 or 2) halogens;

R^4, R^5, and R^6 are each independently selected from hydrogen, halogen, nitro, hydroxy, thio, amino, C_{1-6}-alkyl, and C_{1-6}-alkyloxy, wherein said alkyl or alkyloxy is optionally substituted by one or more (e.g., 1, 2 or 3) groups selected from halogen, hydroxy, cyano, and C_{1-6}-alkyloxy; and

A is a 5- or 6-membered aryl or heteroaryl group (e.g., phenyl or thiazolyl), optionally substituted with 1, 2, or 3 groups independently selected from halogen, hydroxy, thio, amino, nitro, C_{1-6}-alkoxy, and C_{1-6}-alkyl.

2. The method of claim 1, wherein said compound is selected from: quinuclidin-3-yl (2-(4'-fluoro-[1,1'-biphenyl]-3-yl)propan-2-yl)carbamate; (*S*)-quinuclidin-3-yl (2-(2-(4-fluorophenyl)thiazol-4-yl)propan-2-yl)carbamate; and (*S*)-quinuclidin-3-yl (2-(4'-(2-methoxyethoxy)-[1,1'-biphenyl]-4-yl)propan-2-yl)carbamate; and the pharmaceutically acceptable salts and prodrugs thereof.

3. The method of claim 1, wherein said compound is quinuclidin-3-yl (2-(4'-fluoro-[1,1'-biphenyl]-3-yl)propan-2-yl)carbamate.

4. The method of claim 1, wherein said compound is (*S*)-quinuclidin-3-yl (2-(2-(4-fluorophenyl)thiazol-4-yl)propan-2-yl)carbamate.

5. The method of claim 1, wherein said compound is (*S*)-quinuclidin-3-yl (2-(2-(4-fluorophenyl)thiazol-4-yl)propan-2-yl)carbamate in malate salt form.

6. The method of any one of claims 1-5, wherein the subject has Gaucher disease Type 3.

7. The method of any one of claims 1-6, wherein said compound, or pharmaceutically acceptable salt or prodrug thereof, is administered by systemic administration, *e.g.* via a non-parenteral route.

8. The method of claim 7, wherein said compound, or pharmaceutically acceptable salt or prodrug thereof, is administered orally.

9. The method of any one of claims 1-8, wherein the subject undergoes concurrent treatment with enzyme replacement therapy (ERT), e.g., using a glucocerebrosidase (e.g., imiglucerase, velaglucerase, or taliglucerase).

10. The method of any one of claims 1-9, wherein the subject is administered a daily dose of about 1 mg to about 50 mg of the compound, e.g., from 5 to 50 mg, or from 10 to 40 mg, or from 10 to 30 mg, or from 10 to 20 mg, or from 20 to 30 mg, or from 30 to 40 mg, or from 40 to 50 mg, or from 5 to 25 mg, or from 20 to 50 mg, or from 5 to 15 mg, or from 15 to 30 mg, or about 15 mg.

11. The method of any one of claims 1-10, wherein the subject is administered a single daily dose of 15 mg (measured as the quantity of free base) of (*S*)-quinuclidin-3-yl (2-(2-(4-fluorophenyl)thiazol-4-yl)propan-2-yl)carbamate in malate salt form.

12. The method of any one of claims 1-11, wherein the compound is not administered concurrently with a strong or moderate inducer of CYP3A, e.g., rifampin, phenobarbital, or efavirenz.

13. The method of any one of claims 1-12, wherein the subject is an adult or pediatric patient ≥12 years of age with Gaucher disease Type 3 who is stabilized with enzyme replacement therapy (ERT) using imiglucerase for systemic conditions, and wherein the subject is administered a single daily dose of 15 mg (measured as the quantity of free base) of (*S*)-quinuclidin-3-yl (2-(2-(4-fluorophenyl)thiazol-4-yl)propan-2-yl)carbamate in malate salt form.

14. The method of any one of claims 1-13, wherein the method is effective to improve cognitive ability or reduce cognitive deficits, e.g., as measured by a reduction in the time taken to complete the trail-making test (TMT), TMT-A and/or TMT-B, a reduction in the difference between TMT-A time and TMT-B time (TMT-A – TMT-B), for example, a reduction of at least 10%, or at least 20%, or at least 30%, or at least 40%, or at least 50% (e.g., wherein TMT-A decreases by 5-20%, and/or TMT-B decreases by 25-30%, and/or [TMT-A – TMT-B] decreases by 25-30%).

15. The method of any one of claims 1-14, wherein the method results in increased blood flow in the brain (e.g., in one or more of the frontal, occipital, parietal, or temporal lobes), for example, as shown by fMRI imaging.

16. The method of any one of claims 1-15, wherein the method results in increased nodal connectivity in the brain (e.g., between posterior and anterior aspects of the brain, and/or between occipital-parietal structures and frontal, temporal and/or limbic structures, for example, as shown by fMRI imaging).

17. The method of any one of claims 1-16, wherein the method results in enhanced connectivity in brain regions associated with executive function.

18. The method of any one of claims 1-17, wherein the method results in resting-state functional networks with improved connectivity between default mode and medial and frontal networks.

19. The method of any one of claims 1-18, wherein the method results in enhanced connectivity between RSNs 1, 2 and 3 (perception-vision, cognition-language-orthography, cognition space) and RSNs 6, 7 and 8 (sensorimotor, auditory and executive control).

20. A compound, or a pharmaceutically acceptable salt or prodrug thereof, as defined in any one of claims 1 to 5 for use in a method for enhancing neuronal connectivity within the brain of a subject, e.g. a method as defined in any one of claims 6-19.

21. Use of a compound, or a pharmaceutically acceptable salt or prodrug thereof, as defined in any one of claims 1 to 5 in the manufacture of a medicament for enhancing neuronal connectivity within the brain of a subject, e.g. as defined in any one of claims 6-19.

22. A method for increasing brain tissue volume, or preventing or delaying loss of brain tissue volume, in a subject, such as in a subject in need thereof, said method comprising administering to the subject an effective amount of a compound as defined in any one of claims 1-5.

23. The method of claim 22, wherein the method results in an increase in brain tissue volume, or prevention or delay in loss of brain tissue volume, in one or more brain regions selected from: right accumbens, left putamen, left entorhinal cortex, right putamen, right postcentral lobe, left pericalcarine, right amygdala, left cuneus and left lingual.

24. The method of claim 22 or claim 23, wherein the method results in increased brain volume in one or more brain regions associated with executive function.

25. The method of any one of claims 22-24, wherein the increase in brain volume in the one or more brain regions is accompanied by an enhancement in neuronal connectivity within the one or more brain regions, e.g., as shown using functional magnetic resonance imaging (fMRI).

26. The method of any one of claims 22-25, wherein the method results in an increase in the whole brain tissue volume.

27. The method of any one of claims 22-26, wherein the subject and/or administration of the compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof, is as defined in any one of claims 6-13.

28. A compound, or a pharmaceutically acceptable salt or prodrug thereof, as defined in any one of claims 1 to 5 for use in a method as defined in any one of claims 22-27.

29. Use of a compound, or a pharmaceutically acceptable salt or prodrug thereof, as defined in any one of claims 1-5 in the manufacture of a medicament for use in a method as defined in any one of claims 22-27.

30. A method for monitoring the progression or regression of a neurological disorder associated with a lysosome storage disease in a subject, wherein the subject is undergoing a treatment which comprises administering to the subject an effective amount of a compound as defined in any one of claims 1-5, said method comprising measuring brain tissue volume of the subject over a time period during the course of the treatment, e.g. using volumetric magnetic resonance imaging (vMRI), and assessing the extent of any change in brain tissue volume over said time period.

31. The method of claim 30, wherein said time period is from 3 months to 24 months, e.g. 3 months to 12 months, 3 months to 6 months, 6 months to 24 months, 6 months to 18 months, 6 months to 12 months, 12 months to 24 months, or 12 to 18 months.

32. The method of claim 30 or claim 31, wherein, if there is a decrease or absence of an increase in whole brain volume observed over said time period, the method further comprises modifying the treatment by increasing the dosage of the compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof, administered to the subject and reassessing the extent of any change in brain tissue volume after a further time period over the course of the modified treatment with the increased dosage.

33. The method of claim 30 or claim 31, wherein, if there is a decrease or absence of an increase in volumes in three or more of the following brain regions: right accumbens area, left putamen, left entorhinal cortex, right putamen, right postcentral lobe, left pericalcarine , right amygdala, left cuneus and left lingual, observed over said time period, the method further comprises modifying the treatment by increasing the dosage of the compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof, administered to the subject and reassessing the extent of any change in brain tissue volume after a further time period over the course of the modified treatment with the increased dosage.

34. The method of any one of claims 30-33, wherein the subject and/or administration of the compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof, is as defined in any one of claims 6-13.

35. A compound as defined in any one of claims 1-5 for use in a method as defined in any one of claims 30-34.

36. Use of a compound as defined in any one of claims 1-5 in the manufacture of a medicament for treatment in accordance with a method as defined in of any one of claims 30-34.

37. A method for assessing the onset of a neurological disorder associated with a lysosomal storage disease in a subject at risk of developing said neurological disorder, said method comprising:

a) measuring the brain tissue volume of the subject (e.g., using vMRI) and comparing against a reference standard to assess whether brain tissue volume is lower than the reference standard;

b) where the brain tissue volume identified in step (a) is lower than the reference standard, identifying the onset of said neurological disorder;

optionally further comprising: c) commencing treatment of the subject by administering to the subject an effective amount of a compound as defined in any one of claims 1-5, or a pharmaceutically acceptable salt or prodrug thereof.

38. The method of claim 37, wherein the method further comprises administering to the subject a compound as defined in any one of claims 1-5, or a pharmaceutically acceptable salt or prodrug thereof.

39. The method of claim 37 or claim 38, wherein the subject undergoes concurrent treatment with imiglucerase.

40. The method of any one of claims 37-39, wherein the subject has been administered enzyme replacement therapy (e.g., imiglucerase, velaglucerase, and/or taliglucerase) prior to the initiation of any optional treatment with the compound as defined in any one of claims 1-5.

41. The method of any one of claims 37-40, wherein the subject has been administered imiglucerase therapy for at least 6 months (optionally at a stable dose) prior to beginning optional therapy with the compound as defined in any one of claims 1-5.

42. The method of any one of claims 37-41, wherein the method further comprises the step of transitioning the subject from ERT therapy (e.g., imiglucerase, velaglucerase, or taliglucerase) to the optional treatment with the compound as defined in any one of claims 1-5.

43. The method of any one of claims 37-42, wherein the subject has a hemoglobin level of at least 11 g/dL for females and at least 12 g/dL for males; a platelet count of at least 100,000/cubic millimeter; a splenic volume of less than 10 multiples of normal (MN); and/or a hepatic volume of less than 1.5 MN.

44. The method of any one of claims 37-43, wherein measuring of brain tissue volume of the subject is by brain positron emission tomography (PET) or by volumetric magnetic resonance imaging (vMRI).

45. The method of any one of claims 37-44, wherein the subject is found to have brain tissue volume lower than the reference standard.

46. The method of any one of claims 37-45, wherein comparison against the reference standard indicates that the subject has a lower brain tissue volume in one or more brain

regions selected from: right accumbens, left putamen, left entorhinal cortex, right putamen, right postcentral lobe, left pericalcarine, right amygdala, left cuneus, and left lingual.

47. The method of any one of claims 37-46, wherein comparison against the reference standard indicates that the subject has a lower brain tissue volume in one or more brain regions associated with executive function.

48. The method of any one of claims 37-47, wherein comparison against the reference standard indicates that the subject has a lower brain tissue volume in one or more brain regions where loss of neuronal connectivity is assessed to be present, e.g. as shown using functional magnetic resonance imaging (fMRI).

49. The method of any one of claims 37-48, wherein comparison against the reference standard indicates that the subject has a lower whole brain tissue volume.

50. The method of any one of claims 37-49, wherein brain tissue volume of the subject is measured a plurality of times, intermittently or routinely, e.g., weekly, monthly, every 2, 3, 4, 6, 9, 12 months, etc., after the treatment with the compound as defined in any one of claims 1-5 is commenced to assess a change in brain tissue volume.

51. The method of any one of claims 37-50, wherein the subject and/or optional administration of the compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof, is as defined in any one of claims 6-13.

52. A compound as defined in any one of claims 1-5 for use in a method as defined in any one of claims 37-51.

53. Use of a compound as defined in any one of claims 1-5 in the manufacture of a medicament for treatment in accordance with a method of any one of claims 37-52.