CLAIMS

~~What is claimed is:~~

~~1.~~ 1. A ~~method for delivering~~use of a recombinant adeno-associated viral (rAAV) particle ~~to~~ comprising an AAV serotype 2 (AAV2) capsid in the manufacture of a medicament for treating a disorder of the central nervous system of a mammal ~~comprising administering~~, wherein the rAAV particle is formulated for administration to each hemisphere of the striatum, wherein the rAAV particle comprises an rAAV vector ~~encoding~~comprising a heterologous nucleic acid that encodes a therapeutic polypeptide, and wherein the heterologous nucleic acid is expressed in at least the ~~cerebral cortex~~cortical structures and striatum of the mammal.

~~2. A method for delivering a rAAV particle to the central nervous system of a mammal comprising administering the rAAV particle to the striatum, wherein the rAAV particle comprises an rAAV vector encoding a heterologous nucleic acid that is expressed in at least the cerebral cortex and striatum of the mammal and wherein the rAAV particle comprises an AAV serotype 1 (AAV1) capsid.~~
~~A method for delivering a rAAV particle to the central nervous system of a mammal comprising administering the rAAV particle to the striatum~~

~~3.~~ 2. The use of claim 1, wherein the rAAV particle ~~comprises an rAAV vector encoding a heterologous nucleic acid that is expressed in at least the cerebral cortex and striatum of the mammal and wherein the rAAV particle comprises an AAV serotype 2 (AAV2) capsid.~~

~~4. The method of any one of claims 1-3, wherein the mammal is a human.~~
~~5.~~ ~~The method of any one of claims 1-4, wherein the rAAV particle is~~is to be administered to the putamen ~~and the caudate nucleus~~of each hemisphere of the striatum.

~~6. The method of claim 5, wherein the rAAV particle is administered to the putamen and the caudate nucleus of each hemisphere of the striatum.~~

~~7. The method of claim 5 or 6, wherein the rAAV particle is administered to one site in the caudate nucleus and two sites in the putamen.~~

~~8. The method of any one of claims 5-7, wherein the ratio of rAAV particles administered to the putamen to rAAV particles administered to the caudate nucleus is at least about 2:1.~~

~~The method of any one of claims 1-8~~

~~9.~~ 3. The use of claim 1, wherein the heterologous nucleic acid is expressed in the frontal cortex, occipital cortex, and/or layer IV of the mammal.

~~10.~~ 4. The ~~method~~use of claim ~~9, wherein the heterologous nucleic acid is expressed in the prefrontal association cortical areas, the premotor cortex, the primary somatosensory cortical areas, sensory motor cortex, parietal cortex, occipital cortex, and/or primary motor cortex.~~

~~11. The method of any one of claims~~ 1~~-10~~, wherein the rAAV particle undergoes retrograde or anterograde transport in the cerebral cortex.

~~12.~~ 5. The ~~method~~use of ~~any one of claims~~claim 1~~-11~~, wherein the heterologous nucleic acid is further expressed in the thalamus, subthalamic nucleus, globus pallidus, substantia nigra and/or hippocampus.

~~13. The method of any one of claims 1 or 4-12, wherein the rAAV particle comprises an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh8R, AAV9, AAV10, AAVrh10, AAV11, AAV12, AAV2R471A, AAV2/2-7m8, AAV DJ, AAV2 N587A, AAV2 E548A, AAV2 N708A, AAV V708K, a goat AAV, AAV1/AAV2 chimeric, bovine AAV, or mouse AAV capsid rAAV2/HBoV1 serotype capsid.~~

~~14. The method of claim 13, wherein the AAV serotype is AAV1, AAV2, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh8R, AAV9, AAV10, or AAVrh10.~~

~~The method of any one of claims 1-14~~

~~15.~~ 6. The use of claim 1, wherein the rAAV vector comprises the heterologous nucleic acid flanked by one or more AAV inverted terminal repeat (ITR) sequences.

~~16.~~ 7. The ~~method~~use of claim ~~15, wherein the heterologous nucleic acid is flanked by two AAV ITRs.~~

~~17. The method of claim 15 or 16, wherein the AAV ITRs are AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh8R, AAV9, AAV10, AAVrh10, AAV11, AAV12, AAV2R471A, AAV DJ, a goat AAV, bovine AAV, or mouse AAV serotype ITRs.~~

~~18. The method of any one of claims 15-17, wherein the AAV ITRs are AAV2 ITRs.~~

~~19.~~ ~~The method of claim 15 or 16~~6, wherein the ITR and the capsid of the rAAV particle are derived from the same AAV serotype.

~~20.~~ 8. The ~~method of any one of claims 3-12, wherein the ITR and the capsid are derived from AAV2.~~

~~21.~~ ~~The method~~use of claim ~~15 or 16~~6, wherein the ITR and the capsid of the rAAV viral particles are derived from different AAV serotypes.

~~22.~~ 9. The ~~method of any one of claims 2 and 4-12, wherein the ITR is derived from AAV2 and the capsid is derived from AAV1.~~

~~23. The method of any one of claims 1-22, wherein the heterologous nucleic acid is operably linked to a promoter.~~

~~24. The method of claim 23, wherein the promoter expresses the heterologous nucleic acid in a cell of the CNS.~~

~~25. The method of claim 23 or 24, wherein the promoter expresses the heterologous nucleic acid in a brain cell.~~

~~26. The method of any one of claims 23-25, wherein the promoter expresses the heterologous nucleic acid in a neuron and/or a glial cell.~~

~~27. The method claim 26, wherein the neuron is a medium spiny neuron of the caudate nucleus, a medium spiny neuron of the putamen, a neuron of the cortex layer IV and/or a neuron of the cortex layer V.~~

~~28. The method of any one of claims 23-27, wherein the promoter is a CBA promoter, a minimum CBA promoter, a CMV promoter or a GUSB promoter.~~

~~29. The method of any one of claims 23-27, wherein the promoter is inducible.~~

~~30. The method of any one of claims 23-29, wherein the rAAV vector comprises one or more of an enhancer, a splice donor/splice acceptor pair, a matrix attachment site, or a polyadenylation signal.~~

~~31. The method of any one of claims 1-30~~use of claim 1, wherein the rAAV vector is a self-complementary rAAV vector.

~~32. The method of claim 31, wherein the vector comprises a first nucleic acid sequence encoding the heterologous nucleic acid and a second nucleic acid sequence encoding a complement of the heterologous nucleic acid, wherein the first nucleic acid sequence can form intrastrand base pairs with the second nucleic acid sequence along most or all of its length.~~

~~33. The method of claim 32, wherein the first nucleic acid sequence and the second nucleic acid sequence are linked by a mutated AAV ITR, wherein the mutated AAV ITR comprises a deletion of the D region and comprises a mutation of the terminal resolution sequence.~~

~~The method of any one of claims 1-33, wherein the heterologous nucleic acid encodes a~~

~~34.~~ 10. The use of claim 1, wherein the therapeutic polypeptide ~~or therapeutic nucleic~~is amino acid decarboxylase.

~~35.~~ 11. The ~~method~~use of claim ~~34~~10, wherein the heterologous nucleic acid ~~encodes~~ encoding amino acid decarboxylase is operably linked to a ~~therapeutic polypeptide.~~cytomegalovirus immediate early promoter.

~~36. The method of claim 35, wherein the therapeutic polypeptide is an enzyme, a neurotrophic factor, a polypeptide that is deficient or mutated in an individual with a CNS-related disorder, an antioxidant, an anti-apoptotic factor, an anti-angiogenic factor, and an anti-inflammatory factor, alpha-synuclein, acid beta-glucosidase (GBA), beta-galactosidase-1 (GLB1), iduronate-2-sulfatase (IDS), galactosylceramidase (GALC), a mannosidase, alphaD-mannosidase (MAN2B1), beta-mannosidase (MANBA), pseudoarylsulfatase A (ARSA), N-acetylglucosamine-l-phosphotransferase (GNPTAB), acid sphingomyelinase (ASM), Niemann-Pick C protein (NPC1), acid alpha-1,4-glucosidase (GAA), hexosaminidase beta subunit, HEXB, N-sulfoglucosamine sulfohydrolase (MPS3A), N-alphaacetylglucosaminidase (NAGLU), heparin acetyl-CoA, alpha-glucosaminidase Nacetyltransferase (MPS3C), N-acetylglucosamine-6-sulfatase (GNS), alpha-Nacetylgalactosaminidase (NAGA), beta-glucuronidase (GUSB), hexosaminidase alpha subunit (HEXA), huntingtin (HTT), lysosomal acid lipase (LIPA), Aspartylglucosaminidase, Alpha-galactosidase A, Palmitoyl-protein thioesterase, Tripeptidyl peptidase, Lysosomal transmembrane protein, Cysteine transporter, Acid ceramidase, Acid alpha-L-fucosidase, cathepsin A, alpha-L-iduronidase, Arylsulfatase B, Arylsulfatase A, N-acetylgalactosamine6-sulfate, Acid beta-galactosidase, or alpha-neuramidase.~~

~~37. The method of claim 35, wherein the heterologous nucleic acid encodes a therapeutic nucleic acid.~~

~~38. The method of claim 37, wherein the therapeutic nucleic acid is an siRNA, an shRNA, an RNAi, an miRNA, an antisense RNA, a ribozyme or a DNAzyme.~~

~~39. The method of any one of claims 34-38, wherein the therapeutic polypeptide or the therapeutic nucleic acid is used to treat a disorder of the CNS.~~

~~40. The method of claim 39, wherein the disorder of the CNS is a lysosomal storage disease (LSD), Huntington's disease, epilepsy, Parkinson's disease, Alzheimer's disease, stroke, corticobasal degeneration (CBD), corticogasal ganglionic degeneration (CBGD), frontotemporal dementia (FTD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP) or cancer of the brain.~~

~~41. The method of claim 40, wherein the disorder is a lysosomal storage disease selected from the group consisting of Aspartylglusoaminuria, Fabry, Infantile Batten Disease (CNL1), Classic Late Infantile Batten Disease (CNL2), Juvenile Batten Disease (CNL3), Batten form CNL4, Batten form CNL5, Batten form CNL6, Batten form CNL7, Batten form CNL8, Cystinosis, Farber, Fucosidosis, Galactosidosialidosis , Gaucher disease type 1, Gaucher disease type 2, Gaucher disease type 3, GM1 gangliosidosis, Hunter disease, Krabbe disease, a mannosidosis disease, Θ-mannosidosis disease, Maroteaux-Lamy, metachromatic leukodystrophy disease, Morquio A, Morquio B, mucolipidosisII/III disease, Niemann-Pick A disease, Niemann-Pick B disease, Niemann-Pick C disease, Pompe disease, Sandhoff disease, Sanfillipo A disease, Sanfillipo B disease, Sanfillipo C disease, Sanfillipo D disease, Schindler disease, Schindler-Kanzaki, sialidosis, Sly disease, Tay-Sachs disease, and Wolman disease.~~

~~42. The method of any one of claims 1-41, wherein the rAAV particle is in a composition.~~

~~43. The method of claim 42, wherein the composition is a pharmaceutical composition comprising a pharmaceutically acceptable excipient.~~

~~44. The method of any one of claims 1-43, wherein the rAAV particle was produced by triple transfection of a nucleic acid encoding the rAAV vector, a nucleic acid encoding AAV rep and cap, and a nucleic acid encoding AAV helper virus functions into a host cell, wherein the transfection of the nucleic acids to the host cells generates a host cell capable of producing rAAV particles.~~

~~45. The method of any one of claims 1-43, wherein the rAAV particle was produced by a producer cell line comprising one or more of nucleic acid encoding the rAAV vector, a nucleic acid encoding AAV rep and cap, and a nucleic acid encoding AAV helper virus functions.~~

~~The method of any one of claims 1-45, wherein the rAAV particle is~~

~~46.~~ 12. The use of claim 1, wherein the rAAV particle is to be delivered by stereotactic delivery.

~~47.~~ 13. The ~~method~~use of ~~any one of claims~~claim 1~~-45~~, wherein the rAAV particle is to be delivered to the striatum by convection enhanced delivery.

~~48.~~ 14. The ~~method~~use of claim ~~47~~13, wherein the rAAV particle is to be delivered using a ~~CED delivery system.~~

~~49. The method of claim 48, wherein the CED system comprises a cannula and/or a pump.~~

~~50. The method of claim 49, wherein the cannula is a reflux-resistant cannula or a stepped cannula.~~

~~51. The method of claim 50, wherein the pump is a manual pump.~~

~~52. The method of claim 50, wherein the pump is an osmotic pump.~~

~~53. The method of claim 50, wherein the pump is an infusion pump.~~

~~54. A method of treating a disorder of the CNS in a mammal comprising administering an effective amount of a rAAV particle to the mammal by the method of any one of claims 1-53.~~

~~55. A method of treating Huntington's Disease in a mammal comprising administering an effective amount of a rAAV particle to the striatum, wherein the rAAV particle comprises an rAAV vector encoding a heterologous nucleic acid that is expressed in at least the cerebral cortex and striatum of the mammal.~~

~~56. The method of claim 55, wherein the rAAV particle comprises an AAV1 capsid or an AAV2 capsid.~~

~~57. A method of treating Parkinson's Disease in a mammal comprising administering an effective amount of a rAAV particle to the striatum, wherein the rAAV particle comprises an~~

~~rAAV vector encoding a heterologous nucleic acid that is expressed in at least the cerebral cortex and striatum of the mammal.~~

~~58. The method of claim 57, wherein the rAAV particle comprises an AAV2 capsid.~~

~~59. The method of any one of claims 55-58, wherein the mammal is a human.~~

~~60. The method of any one of claims 55-59, wherein the rAAV particle is administered to the putamen and the caudate nucleus of the striatum.~~

~~61. The method of claim 58, wherein the rAAV particle is administered to the putamen and the caudate nucleus of each hemisphere of the striatum.~~

~~62. The method of claim 60 or 61, wherein the rAAV particle is administered to one site in the caudate nucleus and two sites in the putamen.~~

~~63. The method of any one of claims 55-62, wherein the ratio of rAAV particles administered to the putamen to rAAV particles administered to the caudate nucleus is at least about 2:1.~~

~~64. The method of any one of claims 55-63, wherein the heterologous nucleic acid is expressed in the frontal cortex, occipital cortex, and/or layer IV of the mammal.~~

~~65. The method of claim 62, wherein the heterologous nucleic acid is expressed in the prefrontal association cortical areas, the premotor cortex, the primary somatosensory cortical areas, sensory motor cortex, parietal cortex, occipital cortex, and/or primary motor cortex.~~

~~66. The method of any one of claims 55-63, wherein the rAAV particle undergoes retrograde or anterograde transport in the cerebral cortex.~~

~~67. The method of any one of claims 55-66, wherein the heterologous nucleic acid is further expressed in the thalamus, subthalamic nucleus, globus pallidus, substantia nigra and/or hippocampus.~~

~~68. The method of any one of claims 55 or 59-65, wherein the rAAV particle comprises an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh8R, AAV9, AAV10, AAVrh10, AAV11, AAV12, AAV2R471A, AAV2/2-7m8, AAV DJ, AAV2 N587A, AAV2 E548A, AAV2 N708A, AAV V708K, a goat AAV, AAV1/AAV2 chimeric, bovine AAV, or mouse AAV capsid rAAV2/HBoV1 serotype capsid.~~

~~69. The method of claim 68, wherein the AAV serotype is AAV1, AAV2, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh8R, AAV9, AAV10, or AAVrh10.~~

~~70. The method of any one of claims 55-69, wherein the rAAV vector comprises the heterologous nucleic acid flanked by one or more AAV inverted terminal repeat (ITR) sequences.~~

~~71. The method of claim 70, wherein the heterologous nucleic acid is flanked by two AAV ITRs.~~

~~72. The method of claim 70 or 71, wherein the AAV ITRs are AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh8R, AAV9, AAV10, AAVrh10, AAV11, AAV12, AAV2R471A, AAV DJ, a goat AAV, bovine AAV, or mouse AAV serotype ITRs.~~

~~73. The method of any one of claims 70-72, wherein the AAV ITRs are AAV2 ITRs.~~

~~74. The method of claim 70 or 71, wherein the ITR and the capsid of the rAAV particle are derived from the same AAV serotype.~~

~~75. The method of claim 74, wherein the ITR and the capsid are derived from AAV2.~~

~~76. The method of claim 70 or 71, wherein the ITR and the capsid of the rAAV viral particles are derived from different AAV serotypes.~~

~~77. The method of claim 76, wherein the ITR is derived from AAV2 and the capsid is derived from AAV1.~~

78. The method of any one of claims 55-77, wherein the heterologous nucleic acid is operably linked to a promoter.

79. The method of claim 78, wherein the promoter expresses the heterologous nucleic acid in a cell of the CNS.

80. The method of claim 78 or 79, wherein the promoter expresses the heterologous nucleic acid in a brain cell.

81. The method of any one of claims 78-80, wherein the promoter expresses the heterologous nucleic acid in a neuron and/or a glial cell.

82. The method of claim 81, wherein the neuron is a medium spiny neuron of the caudate nucleus, a medium spiny neuron of the putamen, a neuron of the cortex layer IV and/or a neuron of the cortex layer V.

83. The method of any one of claims 78-82, wherein the promoter is a CBA promoter, a minimum CBA promoter, a CMV promoter or a GUSB promoter.

84. The method of any one of claims 78-82, wherein the promoter is inducible.

85. The method of any one of claims 78-84, wherein the rAAV vector comprises one or more of an enhancer, a splice donor/splice acceptor pair, a matrix attachment site, or a polyadenylation signal.

86. The method of any one of claims 55-85, wherein the rAAV vector is a self-complementary rAAV vector.

87. The method of claim 86, wherein the vector comprises a first nucleic acid sequence encoding the heterologous nucleic acid and a second nucleic acid sequence encoding a complement of the heterologous nucleic acid, wherein the first nucleic acid sequence can

~~form intrastrand base pairs with the second nucleic acid sequence along most or all of its length.~~

~~88. The method of claim 87, wherein the first nucleic acid sequence and the second nucleic acid sequence are linked by a mutated AAV ITR, wherein the mutated AAV ITR comprises a deletion of the D region and comprises a mutation of the terminal resolution sequence.~~

~~89. The method of any one of claims 55-88, wherein the heterologous nucleic acid encodes a therapeutic polypeptide or therapeutic nucleic acid.~~

~~90. The method of claim 55, 56 or 58-88, wherein the heterologous nucleic acid encodes a therapeutic polypeptide or a therapeutic nucleic acid that inhibits the expression of HTT or inhibits the accumulation of HTT in cells of the CNS of the mammal.~~

~~91. The method of claim 89 or 90, wherein the heterologous nucleic acid encodes an siRNA, an shRNA, an RNAi, an miRNA, an antisense RNA, a ribozyme or a DNAzyme.~~

~~92. The method of any one of claims 55, 56, or 58-88, wherein the heterologous nucleic acid encodes a miRNA that targets huntingtin.~~

~~93. The method of claim 92, wherein the huntingtin comprises a mutation associated with Huntington's disease.~~

~~94. The method of any one of claims 57-88, wherein the heterologous nucleic acid encodes a therapeutic polypeptide, wherein the therapeutic polypeptide is glial-derived growth factor (GDNF), brain-derived growth factor (BDNF), tyrosine hydroxlase (TH), GTPcyclohydrolase (GTPCH), and/or amino acid decarboxylase (AADC).~~

~~95. The method of any one of claims 55-94, wherein the rAAV particle is in a composition.~~

~~96. The method of claim 95, wherein the composition is a pharmaceutical composition comprising a pharmaceutically acceptable excipient.~~

~~97. The method of any one of claims 55-96, wherein the rAAV particle was produced by triple transfection of a nucleic acid encoding the rAAV vector, a nucleic acid encoding AAV rep and cap, and a nucleic acid encoding AAV helper virus functions into a host cell, wherein the transfection of the nucleic acids to the host cells to generate a host cell capable of producing rAAV particles.~~

~~98. The method of any one of claims 55-96, wherein the rAAV particle was produced by a producer cell line comprising one or more of nucleic acid encoding the rAAV vector, a nucleic acid encoding AAV rep and cap, and a nucleic acid encoding AAV helper virus functions.~~

~~99. The method of any one of claims 55-98, wherein the rAAV particle is delivered by stereotactic delivery.~~

~~100. The method of any one of claims 55-99, wherein the rAAV particle is delivered by~~ convection enhanced delivery~~.~~ system comprising a cannula.

~~101.~~ 15. The ~~method~~use of claim ~~97~~14, wherein the rAAV particle is to be delivered ~~using a CED delivery system.~~

~~102. The method~~in a composition to be administered to the striatum at a rate of ~~claim 101, wherein the CED system comprises a cannula and/or a pump.~~greater than 1 uL/min to about 5 uL/min.

16. The use of claim 15, wherein delivery of the composition is monitored by MRI.

17. The ~~method~~use of claim ~~102~~14, wherein ~~the~~ positioning of the cannula is monitored by MRI.

18. The use of claim 14, wherein more than one cannula is ~~a reflux-resistant~~ used.

~~103.~~ 19. The use of claim 14, wherein the cannula ~~or~~is a stepped cannula.

~~104. The method of claim 102, wherein the pump is a manual pump.~~

~~105. The method of claim 102, wherein the pump is an osmotic pump.~~

~~106. The method of claim 102, wherein the pump is an infusion pump.~~

~~107. A system for expression of a heterologous nucleic acid in the cerebral cortex and striatum of a mammal, comprising~~

~~a) a composition comprising rAAV particles, wherein the rAAV particles comprise a rAAV vector encoding the heterologous nucleic acid; and~~

~~b) a device for delivery of the rAAV particles to the striatum.~~

~~108. The system of claim 107, wherein the rAAV particle comprises an AAV1 capsid or an AAV2 capsid.~~

~~109. The system of claim 107 or 108, wherein the mammal is a human.~~

~~110. The system of any one of claims 107-109, wherein the rAAV particle is administered to the putamen and the caudate nucleus of the striatum.~~

~~111. The system of claim 110, wherein the rAAV particle is administered to the putamen and the caudate nucleus of each hemisphere of the striatum.~~

~~112. The system of any one of claims 107-111, wherein the heterologous nucleic acid is expressed in the frontal cortex, occipital cortex, and/or layer IV of the mammal.~~

~~113. The system of claim 112, wherein the heterologous nucleic acid is expressed in the prefrontal association cortical areas, the premotor cortex, the primary somatosensory cortical areas, sensory motor cortex, parietal cortex, occipital cortex, and/or primary motor cortex.~~

~~114. The system of any one of claims 107-113, wherein the rAAV particle undergoes retrograde or anterograde transport in the cerebral cortex.~~

~~115. The system of any one of claims 107-114, wherein the heterologous nucleic acid is further expressed in the thalamus, subthalamic nucleus, globus pallidus, substantia nigra and/or hippocampus.~~

~~116. The system of any one of claims 107 or 109-115, wherein the rAAV particle comprises an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh8R, AAV9, AAV10, AAVrh10, AAV11, AAV12, AAV2R471A, AAV2/2-7m8, AAV DJ, AAV2 N587A, AAV2 E548A, AAV2 N708A, AAV V708K, a goat AAV, AAV1/AAV2 chimeric, bovine AAV, or mouse AAV capsid rAAV2/HBoV1 serotype capsid.~~

~~117. The system of claim 116, wherein the AAV serotype is AAV1, AAV2, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh8R, AAV9, AAV10, or AAVrh10.~~

~~118. The system of any one of claims 107-117, wherein the rAAV vector comprises the heterologous nucleic acid flanked by one or more AAV inverted terminal repeat (ITR) sequences.~~

~~119. The system of claim 118, wherein the heterologous nucleic acid is flanked by two AAV ITRs.~~

~~120. The system of claim 118 or 119, wherein the AAV ITRs are AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh8R, AAV9, AAV10, AAVrh10, AAV11, AAV12, AAV2R471A, AAV DJ, a goat AAV, bovine AAV, or mouse AAV serotype ITRs.~~

~~121. The system of any one of claims 118-120, wherein the AAV ITRs are AAV2 ITRs.~~

~~122. The system of claim 118 or 119, wherein the ITR and the capsid of the rAAV particle are derived from the same AAV serotype.~~

~~123. The system of claim 122, wherein the ITR and the capsid are derived from AAV2.~~

~~124. The system of claim 118 or 119, wherein the ITR and the capsid of the rAAV viral particles are derived from different AAV serotypes.~~

~~125. The system of claim 124, wherein the ITR is derived from AAV2 and the capsid is derived from AAV1.~~

~~126. The system of any one of claims 107-125, wherein the heterologous nucleic acid is operably linked to a promoter.~~

~~127. The system of claim 126, wherein the promoter expresses the heterologous nucleic acid in a cell of the CNS.~~

~~128. The system of claim 126 or 127, wherein the promoter expresses the heterologous nucleic acid in a brain cell.~~

~~129. The system of any one of claims 126-128, wherein the promoter expresses the heterologous nucleic acid in a neuron or glial cell.~~

~~130. The system of claim 129, wherein the neuron is a medium spiny neuron of the caudate nucleus, a medium spiny neuron of the putamen, a neuron of the cortex layer IV and/or a neuron of the cortex layer V.~~

~~131. The system of any one of claims 126-130, wherein the promoter is a CBA promoter, a minimum CBA promoter, a CMV promoter or a GUSB promoter.~~

~~132. The system of any one of claims 126-130, wherein the promoter is inducible.~~

~~133. The system of any one of claims 126-132, wherein the rAAV vector comprises one or more of an enhancer, a splice donor/splice acceptor pair, a matrix attachment site, or a polyadenylation signal.~~

~~134. The system of any one of claims 107-133, wherein the rAAV vector is a self-complementary rAAV vector.~~

~~135. The system of claim 134, wherein the vector comprises a first nucleic acid sequence encoding the heterologous nucleic acid and a second nucleic acid sequence encoding a complement of the heterologous nucleic acid, wherein the first nucleic acid sequence can~~

~~form intrastrand base pairs with the second nucleic acid sequence along most or all of its length.~~

~~136. The system of claim 135, wherein the first nucleic acid sequence and the second nucleic acid sequence are linked by a mutated AAV ITR, wherein the mutated AAV ITR comprises a deletion of the D region and comprises a mutation of the terminal resolution sequence.~~

~~137. The system of any one of claims 107-136, wherein the heterologous nucleic acid encodes a therapeutic polypeptide or therapeutic nucleic acid.~~

~~138. The system of claim 137, wherein the heterologous nucleic acid encodes a therapeutic polypeptide.~~

~~139. The system of claim 138, wherein the therapeutic polypeptide is an enzyme, a neurotrophic factor, a polypeptide that is deficient or mutated in an individual with a CNS-related disorder, an antioxidant, an anti-apoptotic factor, an anti-angiogenic factor, and an anti-inflammatory factor, alpha-synuclein, acid beta-glucosidase (GBA), beta-galactosidase-1 (GLB1), iduronate 2-sulfatase (IDS), galactosylceramidase (GALC), a mannosidase, alphaD-mannosidase (MAN2B1), beta-mannosidase (MANBA), pseudoarylsulfatase A (ARSA), N-acetylglucosamine-l-phosphotransferase (GNPTAB), acid sphingomyelinase (ASM), Niemann-Pick C protein (NPC1), acid alpha-1,4-glucosidase (GAA), hexosaminidase beta subunit, HEXB, N-sulfoglucosamine sulfohydrolase (MPS3A), N-alphaacetylglucosaminidase (NAGLU), heparin acetyl-CoA, alpha-glucosaminidase Nacetyltransferase (MPS3C), N-acetylglucosamine-6-sulfatase (GNS), alpha-Nacetylgalactosaminidase (NAGA), beta-glucuronidase (GUSB), hexosaminidase alpha subunit (HEXA), huntingtin (HTT), lysosomal acid lipase (LIPA), Aspartylglucosaminidase, Alpha-galactosidase A, Palmitoyl protein thioesterase, Tripeptidyl peptidase, Lysosomal transmembrane protein, Cysteine transporter, Acid ceramidase, Acid alpha-L fucosidase, cathepsin A, alpha-L-iduronidase, Arylsulfatase B, Arylsulfatase A, N-acetylgalactosamine6-sulfate, Acid beta-galactosidase, or alpha-neuramidase.~~

140. The system of claim 138, wherein the heterologous nucleic acid encodes a therapeutic nucleic acid.

141. The system of claim 140, wherein the therapeutic nucleic acid is an siRNA, an shRNA, an RNAi, an miRNA, an antisense RNA, a ribozyme or a DNAzyme.

142. The system of any one of claims 137-141, wherein the therapeutic polypeptide or the therapeutic nucleic acid is used to treat a disorder of the CNS.

143. The system of claim 142, wherein the disorder of the CNS is a lysosomal storage disease (LSD), Huntington's disease, epilepsy, Parkinson's disease, Alzheimer's disease, stroke, corticobasal degeneration (CBD), corticogasal ganglionic degeneration (CBGD), frontotemporal dementia (FTD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP) or cancer of the brain.

144. The system of claim 143, wherein the disorder is a lysosomal storage disease selected from the group consisting of Aspartylglusoaminuria, Fabry, Infantile Batten Disease (CNL1), Classic Late Infantile Batten Disease (CNL2), Juvenile Batten Disease (CNL3), Batten form CNL4, Batten form CNL5, Batten form CNL6, Batten form CNL7, Batten form CNL8, Cystinosis, Farber, Fucosidosis, Galactosidosialidosis , Gaucher disease type 1, Gaucher disease type 2, Gaucher disease type 3, GM1 gangliosidosis, Hunter disease, Krabbe disease, a mannosidosis disease, θ-mannosidosis disease, Maroteaux-Lamy, metachromatic leukodystrophy disease, Morquio A, Morquio B, mucolipidosisII/III disease, Niemann-Pick A disease, Niemann-Pick B disease, Niemann-Pick C disease, Pompe disease, Sandhoff disease, Sanfillipo A disease, Sanfillipo B disease, Sanfillipo C disease, Sanfillipo D disease, Schindler disease, Schindler-Kanzaki, sialidosis, Sly disease, Tay-Sachs disease, and Wolman disease.

145. The system of any one of claims 107-144, wherein the rAAV particle is in a composition.

146. The system of claim 145, wherein the composition is a pharmaceutical composition comprising a pharmaceutically acceptable excipient.

~~147. The system of any one of claims 107-146, wherein the rAAV particle was produced by triple transfection of a nucleic acid encoding the rAAV vector, a nucleic acid encoding AAV rep and cap, and a nucleic acid encoding AAV helper virus functions into a host cell, wherein the transfection of the nucleic acids to the host cells to generate a host cell capable of producing rAAV particles.~~

~~148. The system of any one of claims 107-146, wherein the rAAV particle was produced by a producer cell line comprising one or more of nucleic acid encoding the rAAV vector, a nucleic acid encoding AAV rep and cap, and a nucleic acid encoding AAV helper virus functions.~~

~~149. The system of any one of claims 107-148, wherein the rAAV particle is delivered by stereotactic delivery.~~

~~150. The system of any one of claims 107-149, wherein the rAAV particle is delivered by convection enhanced delivery.~~

~~151. The system of claim 150, wherein the rAAV particle is delivered using a CED delivery system.~~

~~152. The system of claim 151, wherein the CED system comprises a cannula and/or a pump.~~

~~153. The system of claim 152, wherein the cannula is a reflux-resistant cannula or a stepped cannula.~~

~~154. The system of claim 152, wherein the pump is a manual pump.~~

~~155. The system of claim 152, wherein the pump is an osmotic pump.~~

~~156. The system of claim 152, wherein the pump is an infusion pump.~~

~~157. A kit for use in the method of any one of claims 1-106 comprising rAAV particles, wherein the rAAV particles comprise a rAAV vector encoding a heterologous nucleic acid that is expressed in at least the cerebral cortex and striatum of the mammal.~~

~~158. The kit of claim 157, wherein the rAAV particles comprise an AAV serotype 1 (AAV1) capsid.~~

~~159. The kit of claim 158, wherein the rAAV particles comprise an AAV serotype 2 (AAV2) capsid.~~

~~160. A kit for treating Huntington's Disease in a mammal, comprising a composition comprising an effective amount of rAAV particles, wherein the rAAV particles comprise an rAAV vector encoding a heterologous nucleic acid that is expressed in at least the cerebral cortex and striatum of the mammal.~~

~~161. The kit of claim 160, wherein the rAAV particles comprise an AAV serotype 1 (AAV1) capsid or an AAV serotype 2 (AAV2) capsid.~~

~~162. A kit for treating Parkinson's Disease in a mammal, comprising a composition comprising an effective amount of rAAV particles, wherein the rAAV particles comprise an rAAV vector encoding a heterologous nucleic acid that is expressed in at least the cerebral cortex and striatum of the mammal.~~

~~163. The kit of claim 161, wherein the rAAV particles comprise an AAV serotype 1 (AAV1) capsid or an AAV serotype 2 (AAV2) capsid.~~

~~164. The kit of any one of claims 157-163, further comprising a device for delivery of the rAAV particles to the striatum.~~

~~165. The kit of any one of claims 157-164, wherein the rAAV particles are in a composition.~~

166. The kit of claim 165, wherein the composition comprises a buffer and/or a pharmaceutically acceptable excipient.

167. The kit of any one of claims 157-166, further comprising instructions for delivery of the composition of rAAV particles to the striatum.

168. A rAAV particle for use in any one of the methods of claims 1-106.
A rAAV particle for use in delivering

169. 20. A use of a recombinant adeno-associated viral (rAAV) particle to the comprising an AAV serotype 2 (AAV2) capsid in the manufacture of a medicament for treating a disorder of the central nervous system of a mammal, wherein the rAAV particle comprises a rAAV vector encoding a heterologous nucleic acid that is expressed in at least the cerebral cortex and striatum of the mammal.

170. A rAAV particle for use in delivering a recombinant adeno-associated viral (rAAV) particle administration of the rAAV particle comprising an AAV serotype 2 (AAV2) capsid to the central nervous system of a mammal, wherein the rAAV particle comprises a rAAV vector encoding a heterologous nucleic acid that is expressed in at least the cerebral cortex and striatum of the mammal, and wherein the rAAV particle further comprises an AAV serotype 1 (AAV1) capsid. comprising

A using a convection enhanced delivery system comprising a cannula to deliver a composition comprising the rAAV particle for use in delivering a recombinant adeno-associated viral (rAAV) particle to the central nervous system of a mammal, to the putamen of each hemisphere of the striatum at a rate of greater than 1 uL/min to about 5 uL/min,

wherein positioning of the cannula is monitored by MRI,

171. wherein the rAAV particle comprises a an rAAV vector encoding comprising a heterologous nucleic acid that is expressed in at least the cerebral cortex encoding amino acid decarboxylase and striatum of the mammal the rAAV vector is operably linked to a cytomegalovirus immediate early promoter, and wherein the rAAV particle further comprises an AAV serotype 1 (AAV2) capsid.

172. A rAAV particle for use in treating Huntington's Disease in a mammal, wherein the rAAV particle comprises a rAAV vector encoding a heterologous nucleic acid that is expressed in at least the cerebral cortex and striatum of the mammal.

~~173. A rAAV particle for use in treating Parkinson's Disease in a mammal, wherein the rAAV particle comprises a rAAV vector encoding a heterologous nucleic acid that~~ is expressed in at least the ~~cerebral cortex~~cortical structures and striatum of the mammal.

~~174. The rAAV of claim 173, wherein the rAAV particle comprises an AAV2 capsid.~~

~~175. The rAAV particle of any one of claims 169-174, wherein the mammal is a human.~~

~~176. The rAAV particle of any one of claims 169-175, wherein the rAAV particle is for administration to the putamen and the caudate nucleus of the striatum.~~

~~177. The rAAV particle of claim 176, wherein the rAAV particle is for administration to the putamen and the caudate nucleus of each hemisphere of the striatum.~~

~~178. The rAAV particle of any one of claims 169-177, wherein the heterologous nucleic acid is expressed in the frontal cortex, occipital cortex, and/or layer IV of the mammal.~~

~~179. The rAAV particle of claim 178, wherein the heterologous nucleic acid is expressed in the prefrontal association cortical areas, the premotor cortex, the primary somatosensory cortical areas, sensory motor cortex, parietal cortex, occipital cortex, and/or primary motor cortex.~~

~~180. The rAAV particle of any one of claims 169-179, wherein the rAAV particle undergoes retrograde or anterograde transport in the cerebral cortex.~~

~~181. The rAAV particle of any one of claims 169-180, wherein the heterologous nucleic acid is further expressed in the thalamus, subthalamic nucleus, globus pallidus, substantia nigra and/or hippocampus.~~

~~182. The rAAV particle of any one of claims 169, 170 or 175-181, wherein the rAAV particle comprises an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh8R, AAV9, AAV10, AAVrh10, AAV11, AAV12, AAV2R471A, AAV2/27m8, AAV DJ, AAV2 N587A, AAV2 E548A, AAV2 N708A, AAV V708K, a goat AAV, AAV1/AAV2 chimeric, bovine AAV, or mouse AAV capsid rAAV2/HBoV1 serotype capsid.~~

~~183. The rAAV particle of claim 182, wherein the AAV serotype is AAV1, AAV2, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh8R, AAV9, AAV10, or AAVrh10.~~

~~184. The rAAV particle of any one of claims 169-183, wherein the rAAV vector comprises the heterologous nucleic acid flanked by one or more AAV inverted terminal repeat (ITR) sequences.~~

~~185. The rAAV particle of claim 184, wherein the heterologous nucleic acid is flanked by two AAV ITRs.~~

~~186. The rAAV particle of claim 184 or 185, wherein the AAV ITRs are AAV ITRs are AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh8R, AAV9, AAV10, AAVrh10, AAV11, AAV12, AAV2R471A, AAV DJ, a goat AAV, bovine AAV, or mouse AAV serotype ITRs.~~

~~187. The rAAV particle of any one of claims 184-186, wherein the AAV ITRs are AAV2 ITRs.~~

~~188. The rAAV particle of claim 184 or 185, wherein the ITR and the capsid of the rAAV particle are derived from the same AAV serotype.~~

~~189. The rAAV particle of claim 188, wherein the ITR and the capsid are derived from AAV2.~~

~~190. The rAAV particle of claim 184 or 185, wherein the ITR and the capsid of the rAAV viral particles are derived from different AAV serotypes.~~

~~191. The rAAV particle of claim 190, wherein the ITR is derived from AAV2 and the capsid is derived from AAV1.~~

~~192. The rAAV particle of any one of claims 169-171, wherein the heterologous nucleic acid is operably linked to a promoter.~~

~~193. The rAAV particle of claim 192, wherein the promoter expresses the heterologous nucleic acid in a cell of the CNS.~~

194. The rAAV particle of claim 192 or 193, wherein the promoter expresses the heterologous nucleic acid in a brain cell.

195. The rAAV particle of any one of claims 191-194, wherein the promoter expresses the heterologous nucleic acid in a neuron or glial cell.

196. The rAAV particle of claim 195, wherein the neuron is a medium spiny neuron of the caudate nucleus, a medium spiny neuron of the putamen, a neuron of the cortex layer IV and/or a neuron of the cortex layer V.

197. The rAAV particle of any one of claims 192-196, wherein the promoter is a CBA promoter, a minimum CBA promoter, a CMV promoter or a GUSB promoter.

198. The rAAV particle of any one of claims 192-196, wherein the promoter is inducible.

199. The rAAV particle of any one of claims 192-198, wherein the rAAV vector comprises one or more of an enhancer, a splice donor/splice acceptor pair, a matrix attachment site, or a polyadenylation signal.

200. The rAAV particle of any one of claims 169-199, wherein the rAAV vector is a self-complementary rAAV vector.

201. The rAAV particle of claim 200, wherein the vector comprises a first nucleic acid sequence encoding the heterologous nucleic acid and a second nucleic acid sequence encoding a complement of the heterologous nucleic acid, wherein the first nucleic acid sequence can form intrastrand base pairs with the second nucleic acid sequence along most or all of its length.

202. The rAAV particle of claim 200, wherein the first nucleic acid sequence and the second nucleic acid sequence are linked by a mutated AAV ITR, wherein the mutated AAV

ITR comprises a deletion of the D region and comprises a mutation of the terminal resolution sequence.

203. The rAAV particle of any one of claims 169-202, wherein the heterologous nucleic acid encodes a therapeutic polypeptide or therapeutic nucleic acid.

204. The rAAV particle of claim 203, wherein the heterologous nucleic acid encodes a therapeutic polypeptide.

205. The rAAV particle of claim 204, wherein the therapeutic polypeptide is an enzyme, a neurotrophic factor, a polypeptide that is deficient or mutated in an individual with a CNSrelated disorder, an antioxidant, an anti-apoptotic factor, an anti-angiogenic factor, and an anti-inflammatory factor, alpha-synuclein, acid beta-glucosidase (GBA), beta-galactosidase-1 (GLB1), iduronate 2-sulfatase (IDS), galactosylceramidase (GALC), a mannosidase, alphaD-mannosidase (MAN2B1), beta-mannosidase (MANBA), pseudoarylsulfatase A (ARSA), N-acetylglucosamine-l-phosphotransferase (GNPTAB), acid sphingomyelinase (ASM), Niemann-Pick C protein (NPC1), acid alpha-1,4-glucosidase (GAA), hexosaminidase beta subunit, HEXB, N-sulfoglucosamine sulfohydrolase (MPS3A), N-alpha-acetylglucosaminidase (NAGLU), heparin acetyl-CoA, alpha-glucosaminidase N-acetyltransferase (MPS3C), N-acetylglucosamine-6-sulfatase (GNS), alpha-N-acetylgalactosaminidase (NAGA), beta-glucuronidase (GUSB), hexosaminidase alpha subunit (HEXA), huntingtin (HTT), lysosomal acid lipase (LIPA), Aspartylglucosaminidase, Alpha-galactosidase A, Palmitoyl protein thioesterase, Tripeptidyl peptidase, Lysosomal transmembrane protein, Cysteine transporter, Acid ceramidase, Acid alpha-L-fucosidase, cathepsin A, alpha-L-iduronidase, Arylsulfatase B, Arylsulfatase A, N-acetylgalactosamine6-sulfate, Acid beta-galactosidase, or alpha-neuramidase.

206. The rAAV particle of claim 203, wherein the heterologous nucleic acid encodes a therapeutic nucleic acid.

207. The rAAV particle of claim 206, wherein the therapeutic nucleic acid is an siRNA, an shRNA, an RNAi, an miRNA, an antisense RNA, a ribozyme or a DNAzyme.

208. The rAAV particle of any one of claims 203-207, wherein the therapeutic polypeptide or the therapeutic nucleic acid is used to treat a disorder of the CNS.

209. The rAAV particle of claim 208, wherein the disorder of the CNS is a lysosomal storage disease (LSD), Huntington's disease, epilepsy, Parkinson's disease, Alzheimer's disease, stroke, corticobasal degeneration (CBD), corticogasal ganglionic degeneration (CBGD), frontotemporal dementia (FTD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP) or cancer of the brain.

210. The rAAV particle of claim 209, wherein the disorder is a lysosomal storage disease selected from the group consisting of Aspartylglusoaminuria, Fabry, Infantile Batten Disease (CNL1), Classic Late Infantile Batten Disease (CNL2), Juvenile Batten Disease (CNL3), Batten form CNL4, Batten form CNL5, Batten form CNL6, Batten form CNL7, Batten form CNL8, Cystinosis, Farber, Fucosidosis, Galactosidosialidosis , Gaucher disease type 1, Gaucher disease type 2, Gaucher disease type 3, GM1 gangliosidosis, Hunter disease, Krabbe disease, a mannosidosis disease, Θ-mannosidosis disease, Maroteaux-Lamy, metachromatic leukodystrophy disease, Morquio A, Morquio B, mucolipidosisII/III disease, Niemann-Pick A disease, Niemann-Pick B disease, Niemann-Pick C disease, Pompe disease, Sandhoff disease, Sanfillipo A disease, Sanfillipo B disease, Sanfillipo C disease, Sanfillipo D disease, Schindler disease, Schindler-Kanzaki, sialidosis, Sly disease, Tay-Sachs disease, and Wolman disease.

211. The rAAV particle of any one of claims 169-210, wherein the rAAV particle is in a composition.

212. The rAAV particle of claim 211, wherein the composition is a pharmaceutical composition comprising a pharmaceutically acceptable excipient.

213. The rAAV particle of any one of claims 169-212, wherein the rAAV particle was produced by triple transfection of a nucleic acid encoding the rAAV vector, a nucleic acid encoding AAV rep and cap, and a nucleic acid encoding AAV helper virus functions into a host cell, wherein the transfection of the nucleic acids to the host cells to generate a host cell capable of producing rAAV particles.

~~214. The rAAV particle of any one of claims 169-212, wherein the rAAV particle was produced by a producer cell line comprising one or more of nucleic acid encoding the rAAV vector, a nucleic acid encoding AAV rep and cap, and a nucleic acid encoding AAV helper virus functions.~~

~~215. The rAAV particle of any one of claims 169-214, wherein the rAAV particle is delivered by stereotactic delivery.~~

~~216. The rAAV particle of any one of claims 169-214, wherein the rAAV particle is delivered by convection enhanced delivery.~~

~~217. The rAAV particle of claim 216, wherein the rAAV particle is delivered using a CED delivery system.~~

~~218. The rAAV particle of claim 217, wherein the CED system comprises a cannula and/or a pump.~~

~~219. The rAAV particle of claim 218, wherein the cannula is a reflux-resistant cannula or a stepped cannula.~~

~~220. The rAAV particle of claim 218, wherein the pump is a manual pump.~~

~~221. The rAAV particle of claim 218, wherein the pump is an osmotic pump.~~

~~222. The rAAV particle of claim 218, wherein the pump is an infusion pump.~~