METHOD OR SYSTEM OF INFUSING AND/OR PREDICTING AN INFUSATE VOLUME

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 63/618,684 filed January 8, 2024, and U.S. Provisional Patent Application No. 63/729,835 filed December 9, 2024, each of which is hereby incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to a method or system of infusing an infusate volume into a targeted structure and, more particularly, to a method or system of infusing and/or predicting of an infusate volume including a therapeutic agent to obtain a desired percent coverage of a targeted structure (e.g., a putamen).

BACKGROUND OF THE INVENTION

[0003] Existing methods and systems of infusing an infusate into targeted structures have occurred. The targeted structures may include locations in the brain of a subject, including, but not limited to, the putamen. Many of these methods and systems of infusing an infusate use a cannula. Some problems with these infusions have been to accurately determine and predict how much of the infusate should be infused and where exactly the infusion(s) should occur to obtain a prescriptive delivery. Some methods have included using magnetic resonance imaging (MRI) to visually determine how much and where the infusate is being administered.

[0004] It would be desirable to provide an efficient method and system to predict and delivery the infusate to the targeted structure.

SUMMARY OF THE INVENTION

[0005] The term embodiment and like terms are intended to refer broadly to all of the subject matter of this disclosure and the claims below. Statements containing these terms should be understood not to limit the subject matter described herein or to limit the meaning or scope of the claims below. Embodiments of the present disclosure covered herein are defined by the claims below, not this summary. This summary is a high-level overview of various aspects of the disclosure and introduces some of the concepts that are further described in the Detailed Description section below. This summary is not intended to identify key or essential

features of the claimed subject matter. This summary is also not intended to be used in isolation to determine the scope of the claimed subject matter. The subject matter should be understood by reference to appropriate portions of the entire specification of this disclosure, any or all drawings and each claim.

[0006] According to one aspect of the present disclosure, a system to determine segmental infusion volumes ($Vi_{1(t)} + Vi_{2(t)} \ldots + Vi_{n(t)}$) of an infusate to individually administer to each of a plurality of target segmental regions of a target putamen of a subject to achieve a desired percent coverage of the infusate within the target putamen includes an input interface, a storage device, a processor and an output interface. The input interface is configured to receive data on a target putaminal volume ($Vp_{(t)}$) of the target putamen, a number of the plurality of target segmental regions of the target putamen, and the desired percent coverage. The storage device stores: (1) sample putaminal volumes ($Vp_{(s)}$) obtained from sample putamina from a set of sample subjects wherein each sample putamen has a plurality of sample segmental regions; (2) sample infusion volumes ($Vi_{(s)}$) of the infusate infused to each sample segmental region of each sample putamen, wherein a sum of the sample infusion volumes infused into each of the sample segmental regions of each sample putamen is a total sample infusion volume ($Vi_{1(s)} + Vi_{2(s)} \ldots + Vi_{n(s)} = Vi_{T(s)}$); (3) sample volumes of distribution ($Vd_{(s)}$) of the infusate for each sample putamen in which each sample volume of distribution ($Vd_{(s)}$) is a volume of the total sample infusion volume ($Vi_{T(s)}$) retained within each sample putamen; and (4) a sample percent coverage for the infusate in each sample putamen in which each sample percent coverage is calculated by dividing each sample volume of distribution ($Vd_{(s)}$) by the corresponding sample putaminal volume ($Vp_{(s)}$). The processor is coupled to the input interface and the storage device. The processor is configured to determine the total infusion volume ($Vi_{1(t)} + Vi_{2(t)} \ldots + Vi_{n(t)} = Vi_{(T)}$) of the infusate to infuse into the target putamen and the infusion volumes ($Vi_{1(t)} + Vi_{2(t)} \ldots + Vi_{n(t)}$) to infuse into each target segmental region of the target putamen based on: (a) the desired percent coverage; (b) the number of the plurality of target segmental regions of the target putamen; (c) the target putaminal volume ($Vp_{(t)}$); and (d) a plurality of stored sample data selected from the following: the sample putaminal volumes ($Vp_{(s)}$), a number of sample segmental regions per sample putamen, the sample infusion volumes, the total sample infusion volumes, the sample volumes of distribution, the sample percent coverages, and combinations thereof. The output interface is coupled to the processor. The output interface provides the total infusion volume ($Vi_{(T)}$) of the infusate to administer to the target putamen and the segmental infusion volumes to individually administer to each of the plurality of

target segmental regions of the target putamen to achieve the desired percent coverage of the infusate.

[0007] According to a configuration of the above implementation, the processor is further configured to determine sample volumes of distribution; determine the total sample infusion volume ratio ($Vd_{(s)}/Vi_{T(s)}$ ratio); and determine the total infusion volume ($Vi_{(T)}$) of the infusate to administer to the target putamen to achieve the desired percent coverage using the $Vd_{(s)}/Vi_{T(s)}$ ratio. The $Vd_{(s)}/Vi_{T(s)}$ ratio in one embodiment may be from about 1.5 to about 2.5, or in another embodiment may be from about 2 to about 2.25.

[0008] According to another configuration of the above implementation, the target putaminal volume of the subject is determined by magnetic resonance imaging (MRI).

[0009] According to a further configuration of the above implementation, the desired percent coverage by the infusate in the target putamen is from about 40% to about 90% of the target putaminal volume ($Vp_{(T)}$). In another embodiment, the desired percent coverage by the infusate in the target putamen is from about 40% to about 90% of the target putaminal volume ($Vp_{(T)}$).

[0010] According to one method of the present disclosure, segmental infusion volumes of an infusate are determined for infusion into each of a plurality of target segmental regions of a target putamen of a subject in need thereof to achieve a desired percent coverage of the infusate within the target putamen using a system including an input interface, a storage device, a processor and an output interface. The processor is coupled to the input interface and the storage device. The output interface is coupled to the processor. The method includes entering a target putaminal volume ($Vp_{(t)}$) of the target putamen, a number of target segmental regions of the target putamen, and the desired percent coverage into the input interface of the system. The output interface receives the total infusion volume ($Vi_{(t)}$) of the infusate and the segmental infusion volumes to individually administer to each of the plurality of target segmental regions of the target putamen to achieve the desired percent coverage of the infusate.

[0011] In a further aspect of the above method, the segmental infusion volumes of the infusate are infused to each of the plurality of target segmental regions of the target putamen. The infusing may be performed without magnetic resonance imaging (MRI). The infusing may be performed with a syringe pump.

[0012] In a further aspect of the above method, a cannula is inserted through a brain of the subject to the target putamen. A first segmental infusion volume of the infusate is infused into the first segmental region. The distal end of the cannula is advanced to a second

segmental region and a second segmental infusion volume of the infusate is infused into the second segmental region. The advancing and infusing steps are repeated until each of the plurality of target segmental regions has been infused with the infusate.

[0013] In another aspect of the above method, the infusing may be performed with a cannula that is capable of infusing the infusate to the plurality of target segmental regions simultaneously. The infusing may be performed with a syringe pump.

[0014] In a further aspect of the above method, the cannula comprises a stylet that is removeable from the cannula without removing the cannula from the target putamen. The cannula may be inserted into the brain using MRI guidance, and MRI is not utilized during the infusing.

[0015] In another aspect of the above method, the total infusion volume ($Vi_{(T)}$) of the infusate is delivered to a posterior segmental region of the target putamen, a middle segmental region of the target putamen, and an anterior segmental region of the target putamen.

[0016] In a further aspect of the above method, the total infusion volume ($Vi_{(T)}$) of the infusate includes a first infusion volume ($Vi_{1(t)}$), a second infusion volume ($Vi_{2(t)}$), and a third infusion volume ($Vi_{3(t)}$). In one embodiment, the first infusion volume ($Vi_{1(t)}$) is from about 10% to about 30% of the total infusion volume ($Vi_{(T)}$), the second infusion volume ($Vi_{2(t)}$) is from about 30% to about 50% of the total infusion volume ($Vi_{(T)}$), and the third infusion volume ($Vi_{3(t)}$) is from about 30% to about 50% of the total infusion volume ($Vi_{(T)}$). The first infusion volume ($Vi_{1(t)}$) in another embodiment is from about 15% to about 25% of the total infusion volume ($Vi_{(T)}$), the second infusion volume ($Vi_{2(t)}$) is from about 35% to about 40% of the total infusion volume ($Vi_{(T)}$), and the third infusion volume ($Vi_{3(t)}$) is from about 40% to about 45% of the total infusion volume ($Vi_{(T)}$). In another embodiment, the first infusion volume ($Vi_{1(t)}$) is calculated to be delivered to a posterior segmental region of the target putamen, the second infusion volume ($Vi_{2(t)}$) is calculated to be delivered to a middle segmental region of the target putamen, and the third infusion volume ($Vi_{3(t)}$) is calculated to be delivered to an anterior segmental region of the target putamen.

[0017] In another aspect of the above method, the desired percent coverage by the infusate in the target putamen is from about 40% to about 90% of the target putaminal volume ($Vp_{(T)}$). In another aspect of the above method, the desired percent coverage by the infusate in the target putamen is from about 50% to about 80% of the target putaminal volume ($Vp_{(T)}$).

[0018] According to a further aspect of the present disclosure, a system to determine a total infusion volume ($Vi_{(T)}$) of an infusate to administer to a target putamen of a subject to achieve a desired percent coverage of the infusate within the target putamen includes an input

interface, a storage device, a processor and an output device. The input interface is configured to receive data on a target putaminal volume ($Vp_{(t)}$) of the target putamen and the desired percent coverage. The storage device stores: (1) sample putaminal volumes ($Vp_{(s)}$) obtained from sample putamina from a set of sample subjects; (2) a total sample infusion volume ($Vi_{T(s)}$) of the infusate to each sample putamen; (3) sample volumes of distribution ($Vd_{(s)}$) being a volume of the total sample infusion volume ($Vi_{T(s)}$) retained within each sample putamen; and (4) a sample percent coverage for the infusate in each sample putamen by dividing each sample volume of distribution ($Vd_{(s)}$) by the corresponding sample putaminal volume ($Vp_{(s)}$). The processor is coupled to the input interface and the storage device. The processor is configured to determine the total infusion volume ($Vi_{(T)}$) of the infusate to infuse into the target putamen based on the target putaminal volume ($Vp_{(t)}$) of the subject, the desired percent coverage, and a plurality of stored sample data selected from the following: the sample putaminal volumes ($Vp_{(s)}$), the total sample infusion volumes ($Vi_{T(s)}$), the sample volumes of distribution ($Vd_{(s)}$), the sample percent coverages, and combinations thereof. The output interface is coupled to the processor. The output interface provides the total infusion volume ($Vi_{(T)}$) of the infusate to administer to the target putamen to achieve the desired percent coverage of the infusate.

[0019] According to a configuration of the above implementation, the system further includes an infusion control system configured to regulate infusion of the infusate to the target putamen. The infusion control system includes at least one pump to infuse the infusate at a determined rate of infusion for the total infusion volume ($Vi_{(T)}$). The infusion control system may include a cannula to allow simultaneous infusion of the infusate into two or more target segmental regions of the target putamen.

[0020] According to a further aspect of the present disclosure, the system may further include a display coupled to the output interface. The display is operable to display the total infusion volume ($Vi_{(T)}$) of the infusate.

[0021] In a further aspect of the above implementation, the desired percent coverage by the infusate in the target putamen is from about 40% to about 90% of the target putaminal volume ($Vp_{(T)}$). The desired percent coverage by the infusate in the target putamen in another embodiment is from about 50% to about 80% of the target putaminal volume ($Vp_{(T)}$).

[0022] According to one method of the present disclosure, a training set to a machine learning model to predict a total infusion volume ($Vi_{(T)}$) of an infusate to administer to each of a plurality of target segmental regions of a target putamen of a subject to achieve a desired percent coverage of the infusate within the target putamen is provided. The method includes

obtaining sample putaminal volumes ($Vp_{(s)}$) from a set of sample subjects by scanning each putamen of each of the set of sample subjects via a scanner. Each sample putamen has a plurality of sample segmental regions. At least one sample infusion volume ($Vi_{(s)}$) of the infusate is infused to each sample segmental region of each sample putamen via a cannula. A volume of each of the at least one sample infusion volume ($Vi_{(s)}$) retained within each sample segmental region is a sample volume of distribution ($Vd_{(s)}$) of the infusate. A sum of the at least one sample infusion volume for each of the plurality of sample segmental regions infused into each sample putamen is a total sample infusion volume ($Vi_{1(s)} + Vi_{2(s)} \ldots + Vi_{n(s)} = Vi_{T(s)}$) and a volume of the total sample infusion volume ($Vi_{T(s)}$) retained within each sample putamen is the sample volume of distribution ($Vd_{(s)}$). A sample percent coverage for the infusate is determined in each sample putamen by dividing each sample volume of distribution ($Vd_{(s)}$) by the corresponding sample putaminal volume ($Vp_{(s)}$). The total infusion volume ($Vi_{(T)}$) of the infusate is determined to administer to the plurality of target segmental regions of the target putamen to achieve the desired percent coverage of the infusate based on a target putaminal volume ($Vp_{(T)}$) and a plurality of sample data selected from the following: the sample putaminal volumes ($Vp_{(s)}$), a number of sample segmental regions per sample putamen, the sample infusion volumes ($Vi_{(s)}$), the total sample infusion volumes ($Vi_{(T)}$), the sample volumes of distribution ($Vd_{(s)}$), the sample percent coverages, and combinations thereof. The training set is prepared having inputs of the determined sample putaminal volumes, the determined total sample infusion volumes, the determined total sample volumes of distribution, and the determined sample percent coverage. A machine learning model is trained via the training set to predict the total infusion volume of the infusate based on inputs of the target putaminal volume and the desired sample percent coverage of the infusate.

[0023] According to a configuration of the above method, the infusate comprises a contrast agent and the sample volumes of distribution ($Vd_{(s)}$) are determined by visualizing the contrast agent in the infusate by magnetic resonance imaging (MRI).

[0024] According to another configuration of the above method, the sample volumes of distribution ($Vd_{(s)}$) are determined after all of the at least one sample infusion volumes have been infused into each of the sample putamina.

[0025] According to one method of the present disclosure, a computer-implemented method to predict a plurality of infusion volumes ($Vi_{(T)}$) of an infusate to administer to each of a plurality of target segmental regions of a target putamen of a subject to achieve a desired percent coverage of the infusate within the target putamen including determining sample putaminal volumes ($Vp_{(s)}$) from a set of sample subjects. Each sample putamen has a

plurality of sample segmental regions. A sample percent coverage is determined for the infusate in each sample putamen by dividing each total sample volume of distribution ($Vd_{(s)}$) by the corresponding sample putaminal volume ($Vp_{(s)}$) via a processor. Each sample volume of distribution is obtained from infusing a sample infusion volume ($Vi_{(s)}$) of the infusate to each sample segmental region of each sample putamen via a cannula. A volume of each sample infusion volume ($Vi_{(s)}$) retained within each sample segmental region is a sample volume of distribution ($Vd_{(s)}$). A sum of the at least one sample infusion volume for each of the plurality of segmental regions infused into each sample putamen is a total sample infusion volume ($Vi_{1(s)} + Vi_{2(s)} \ldots + Vi_{n(s)} = Vi_{T(s)}$) and a volume of the total sample infusion volume ($Vi_{T(s)}$) retained within each sample putamen is the sample volume of distribution ($Vd_{(s)}$). The total infusion volume ($Vi_{(T)}$) of the infusate is determined via a processor to administer to the plurality of target segmental regions of the target putamen to achieve the desired coverage of the infusate based on a target putaminal volume ($Vp_{(t)}$) and a plurality of sample factors selected from the following: the sample putaminal volumes ($Vp_{(s)}$), a number of sample segmental regions per sample putamen, the sample infusion volumes ($Vi_{(s)}$), the total sample infusion volumes ($Vi_{(T)}$), the sample volumes of distribution ($Vd_{(s)}$), the sample percent coverages, and combinations thereof.

[0026] In a further aspect of the above method, an infusion time and an infusion rate are determined for infusing the total infusion volume ($Vi_{(T)}$) of the infusate via the processor.

[0027] In a further aspect of the above method, the infusate includes a therapeutic agent being selected from the group consisting of a viral therapeutic, a DNA therapeutic, an RNA therapeutic, a protein therapeutic, therapeutic nanoparticles, and a small molecule compound.

[0028] In another aspect of the above method, the sample infusion volume ($Vi_{(s)}$) is delivered to at least two of the plurality of segmental regions of each sample putamen via the cannula. The sample infusion volume ($Vi_{(s)}$) may be delivered to at least three of the plurality of segmental regions of each sample putamen via the cannula in another embodiment.

[0029] In a further aspect of the above method, the plurality of segmental regions of each sample putamen is selected from the group consisting of a posterior segmental region of the putamen, a middle segmental region of the putamen, an anterior segmental region of the putamen, and combinations thereof.

[0030] In a further aspect of the above method, a first sample infusion volume ($Vi_{1(s)}$) is delivered to a first segmental region of each sample putamen via the cannula and a second sample infusion volume ($Vi_{2(s)}$) is delivered to each second segmental region of the sample putamen via the cannula. The first and second sample infusion volumes of each sample

putamen provide a respective total sample infusion volume.

[0031] In a further aspect of the above method, a first sample infusion volume ($Vi_{1(s)}$) is delivered to a first segmental region of each sample putamen via the cannula, a second sample infusion volume ($Vi_{2(s)}$) is delivered to a second segmental region of each sample putamen via the cannula, and a third sample infusion volume ($Vi_{3(s)}$) is delivered to a third segmental region of each sample putamen via the cannula. The first, second and third sample infusion volumes of each sample putamen provide a respective total sample infusion volume ($Vi_{T(s)}$).

[0032] In another aspect of the above method, the desired percent coverage by the infusate in the target putamen is from about 40% to about 90% of the target putaminal volume ($Vp_{(t)}$).

[0033] In a further aspect of the above method, the total infusion volume ($Vi_{(T)}$) of the infusate includes a first infusion volume ($Vi_{1(t)}$), a second infusion volume ($Vi_{2(t)}$), and a third infusion volume ($Vi_{3(t)}$).

[0034] In a further aspect of the above method, the first infusion volume ($Vi_{1(t)}$) is from about 10% to about 30% of the total infusion volume ($Vi_{(T)}$), the second infusion volume ($Vi_{2(t)}$) is from about 30% to about 50% of the total infusion volume ($Vi_{(T)}$), and the third infusion volume ($Vi_{3(t)}$) is from about 30% to about 50% of the total infusion volume ($Vi_{(T)}$). In another embodiment, the first infusion volume ($Vi_{1(t)}$) is from about 15% to about 25% of the total infusion volume ($Vi_{(T)}$), the second infusion volume ($Vi_{2(t)}$) is from about 35% to about 40% of the total infusion volume ($Vi_{(T)}$), and the third infusion volume ($Vi_{3(t)}$) is from about 40% to about 45% of the total infusion volume ($Vi_{(T)}$). In a further embodiment, the first infusion volume ($Vi_{1(t)}$) is calculated to be delivered to a posterior segmental region of the target putamen, the second infusion volume ($Vi_{2(t)}$) is calculated to be delivered to a middle segmental region of the target putamen, and the third infusion volume ($Vi_{3(t)}$) is calculated to be delivered to an anterior segmental region of the target putamen.

[0035] In a further aspect of the above method, the infusion volume of the infusate is infused via the cannula. The infusing includes simultaneous infusion of the infusate in a posterior segmental region of the target putamen, a middle segmental region of the target putamen, and an anterior segmental region of the target putamen.

[0036] In another aspect of the above method, the sample putaminal volumes ($Vp_{(s)}$) is determined from a set of sample subjects is performed by scanning each putamen of each of the set of sample subjects via a scanner. The scanner is a magnetic resonance imaging (MRI) scanner.

[0037] In a further aspect of the above method, the sample volume of distribution ($Vd_{(s)}$) for

each sample putamen is determined by a magnetic resonance imaging (MRI) scanner.

[0038] In a further aspect of the above method, the total infusion volume ($Vi_{(T)}$) of the infusate is verified with a desired clinical outcome for a therapeutic agent in the infusate. The desired clinical outcome may be an improvement identified during a treatment of a central nervous system (CNS) disorder.

[0039] According to a further aspect of the present disclosure, a system for determining a first infusion volume ($Vi_{1(t)}$), a second infusion volume ($Vi_{2(t)}$), and a third infusion volume ($Vi_{3(t)}$) of an infusate to infuse into a first target segmental region, a second target segmental region, and a third target segmental region of a subject's target putamen having only three target segmental regions, respectively, in order to achieve a desired percent coverage of the infusate of at least about 40% of the target putamen in the subject includes an input interface, a storage device, a processor and an output interface. The input interface is configured to receive data on a target putaminal volume ($Vp_{(t)}$) of the target putamen measured by MRI, a number of the plurality of target segmental regions of the target putamen, and the desired percent coverage. The storage device stores the following for each of a plurality of sample putamina: (1) sample putaminal volumes ($Vp_{(s)}$) obtained from sample putamina from a set of sample subjects, each sample putamen having a first sample segmental region, a second sample segmental region, and a third sample segmental region; (2) first sample infusion volumes ($Vi_{1(s)}$) of the infusate individually infused into each first sample segmental region, second sample infusion volumes ($Vi_{2(s)}$) of the infusate individually infused into each second sample segmental region, and third sample infusion volumes ($Vi_{3(s)}$) of the infusate individually infused into each third sample segmental region in which a sum of the first, second, and third sample infusion volumes is a total sample infusion volume ($Vi_{1(s)} + Vi_{2(s)} + Vi_{3(s)} = Vi_{T(s)}$); (3) sample volumes of distribution ($Vd_{(s)}$) of the infusate for each putamen in which each sample volume of distribution ($Vd_{(s)}$) is a volume of the total sample infusion volume ($Vi_{T(s)}$) retained within each sample putamen; and (4) a sample percent coverage for the infusate in each sample putamen in which each sample percent coverage is calculated by dividing each sample volume of distribution ($Vd_{(s)}$) by the corresponding sample putaminal volume ($Vp_{(s)}$). A processor is coupled to the input interface and the storage device. The processor is configured to determine the total infusion volume ($Vi_{(T)}$) of the infusate to infuse into the target putamen and the first, second, and third infusion volumes ($Vi_{1(t)} + Vi_{2(t)} + Vi_{3(t)} = Vi_{(T)}$) to infuse into each target segmental region of the target putamen based on: (a) the desired percent coverage; (b) the first, second, and third target segmental regions of the target putamen; (c) the target putaminal volume ($Vp_{(t)}$); and (d) a plurality of stored sample

data selected from the following: the sample putaminal volumes ($Vp_{(s)}$), the first, second, and third sample segmental regions per sample putamen, the first, second, and third sample infusion volumes ($Vi_{(s)}$), the total sample infusion volumes ($Vi_{(T)}$), the sample volumes of distribution ($Vd_{(s)}$), and the sample percent coverages. The output interface provides the total infusion volume ($Vi_{(T)}$) of the infusate to administer to the target putamen and the first, second, and third infusion volumes ($Vi_{1(t)}$, $Vi_{2(t)}$, $Vi_{3(t)}$) to administer to the first, second, and third target segmental regions, respectively, to achieve the desired percent coverage of the infusate. The first infusion volume ($Vi_{1(t)}$) is from about 10% to about 30% of the total infusion volume ($Vi_{(T)}$). The second infusion volume ($Vi_{2(t)}$) is from about 30% to about 50% of the total infusion volume ($Vi_{(T)}$). The third infusion volume ($Vi_{3(t)}$) is from about 30% to about 50% of the total infusion volume ($Vi_{(T)}$).

[0040] According to a configuration of the above implementation, the first infusion volume ($Vi_{1(t)}$) is from about 15% to about 25% of the total infusion volume ($Vi_{(T)}$), the second infusion volume ($Vi_{2(T)}$) is from about 35% to about 40% of the total infusion volume ($Vi_{(T)}$), and the third infusion volume ($Vi_{3(T)}$) is from about 40% to about 45% of the total infusion volume ($Vi_{(T)}$). In another embodiment, the first infusion volume ($Vi_{1(T)}$) is about 20% of the total infusion volume ($Vi_{(T)}$), the second infusion volume ($V_{2(T)}$) is about 37% of the total infusion volume ($Vi_{(T)}$), and the third infusion volume ($Vi_{3(T)}$) is about 43% of the total infusion volume ($Vi_{(T)}$).

[0041] According to another configuration of the above implementation, a first target segmental region of the target putamen, a second target segmental region of the target putamen, and a third target segmental region of the target putamen correspond to the first sample segmental region of the sample putamen, the second sample segmental region of the sample putamen, and the third sample segmental region of the sample putamina, respectively.

[0042] In a further aspect of the above implementation, the first target segmental region of the target putamen is a posterior segmental region of the target putamen, a second target segmental region of the target putamen is a middle segmental region of the target putamen, and a third target segmental region of a target putamen is an anterior segmental region of the target putamen.

[0043] In a further aspect of the above implementation, the first infusion volume ($Vi_{1(T)}$) is to be delivered to the posterior segmental region of the target putamen, the second infusion volume ($Vi_{2(T)}$) is to be delivered to a middle segmental region of the target putamen, and the third infusion volume ($Vi_{3(T)}$) is to be delivered to an anterior segmental region of the target putamen.

[0044] In another method, a total infusion volume ($Vi_{(t)}$) of an infusate is implemented into a target putamen of a subject in need thereof to achieve an infusate coverage of at least 40% in the target putamen. The method includes providing a distance from a posterior end of the target putamen to an anterior end of the target putamen. The distance is along a longitudinal axis of the target putamen. Locations of a predetermined number of a plurality of infusion sites is determined along the longitudinal axis based on the distance. The total infusion volume ($Vi_{(t)}$) of the infusate to be infused into the target putamen is provided. The total infusion volume is greater than 1000 μL. A plurality of segmental infusion volumes is determined. Each segmental infusion volume of the plurality to be infused into a corresponding infusion site is selected from the plurality of infusion sites. A sum of the plurality of segmental infusion volumes is the total infusion volume ($Vi_{(t)}$). A cannula is inserted through a brain of the subject and the cannula is positioned in the target putamen. Each of the plurality of segmental infusion volumes of the infusate is infused into each of the corresponding plurality of infusion sites of the target putamen.

[0045] In a further aspect of the above method, the plurality of segmental infusion volumes is determined based on a database derived from sample segmental infusion volumes infused into sample infusion sites of sample putamens resulting in sample coverages.

[0046] In a further aspect of the above method accurate placement of the cannula in the target putamen is verified using intraoperative computed tomography (CT).

[0047] A further aspect of the above method includes infusing a first segmental infusion volume ($Vi_{(1)}$) of the infusate into a first infusion site; advancing a distal end of the cannula to a second infusion site and infusing a second segmental infusion volume ($Vi_{(2)}$) of the infusate into the second infusion site; and repeating the advancing and infusion steps until each of the plurality of infusion sites has been infused with the infusate.

[0048] A further aspect of the above method includes infusing a first segmental infusion volume ($Vi_{(1)}$) of the infusate into the first infusion site; advancing a distal end of the cannula to a second infusion site and infusing a second segmental infusion volume ($Vi_{(2)}$) of the infusate into the second infusion site; and advancing the distal end of the cannula to a third infusion site and infusing a third segmental infusion volume ($Vi_{(3)}$) of the infusate into the third infusion site. The distal end of the cannula may be advanced to a fourth infusion site with a fourth segmental infusion volume ($Vi_{(4)}$) of the infusate being infused into the fourth infusion site.

[0049] In a further aspect of the above method, the infusate coverage by the infusate in the target putamen is from about 40% to about 90% of the volume of the target putamen of the

subject. The infusate coverage by the infusate in the target putamen may be from about 50% to about 80% of the volume of the target putamen of the subject.

[0050] In a further aspect of the above method, the infusing is performed with a syringe pump.

[0051] In a further aspect of the above method, the infusion occurs only at the plurality of infusion sites.

[0052] In a further aspect of the above method, the cannula comprises a stylet and further includes removing the stylet without removing the cannula from the target putamen of the subject.

[0053] A further aspect of the above method includes measuring the infusate coverage by the infusate in the target putamen after the total infusion volume ($Vi_{(T)}$) of the infusate has been infused.

[0054] In a further aspect of the above method, the infusate coverage is measured using MRI.

[0055] In a further aspect of the above method, the total infusion volume ($Vi_{(T)}$) delivered to the target putamen is greater than 1200μL. The total infusion volume ($Vi_{(T)}$) delivered to the target putamen is greater than 1400μL in another embodiment. The total infusion volume ($Vi_{(T)}$) delivered to the target putamen is from about 1,000 to about 2,000μL in a further embodiment. The total infusion volume ($Vi_{(T)}$) delivered to the target putamen is from about 1,300 to about 1,800μL in yet another embodiment.

[0056] In a further aspect of the above method, the infusate is infused to the plurality of infusion sites at a rate of from about 2 to about 12 μL/min. The rate may be from about 3 to about 10 μL/min.

[0057] In a further aspect of the above method, the predetermined number of the plurality of infusion sites is 4, and where: a first infusion site is from 3 mm to 8 mm from the posterior end of the target putamen; a fourth infusion site is from 5 mm to 15 mm from the anterior end of the target putamen; and a second infusion site and a third infusion site are 1/3 and 2/3 of a distance between the first and fourth infusion sites, respectively. The plurality of segmental infusion volumes may be 4 infusion volumes in which each of the 4 infusion volumes to be infused into one of the 4 infusion sites, and wherein: a first segmental infusion volume is from 5% to 20% of the total infusion volume; a second segmental infusion volume is from 25% to 35% of the total infusion volume; a third segmental infusion volume is from 25% to 35% of the total infusion volume; and a fourth segmental infusion volume is from 10% to 30% of the total infusion volume. This may include infusing the first segmental infusion volume of the infusate into the first infusion site; infusing the second segmental infusion

volume of the infusate into the second infusion site; infusing the third segmental infusion volume of the infusate into the third infusion site; and infusing the fourth segmental infusion volume of the infusate into the fourth infusion site. The total infusion volume is about 1500 μL with the first segmental infusion volume being about 150 μL; the second segmental infusion volume being about 500 μL; the third segmental infusion volume being about 500 μL; and the fourth segmental infusion volume being about 350 μL. The cannula may be positioned using preoperative imaging scans and without real-time MRI guidance.

[0058] In yet another method, a total infusion volume ($Vi_{(t)}$) of an infusate is implemented into a target putamen of a subject in need thereof to achieve a therapeutically effective coverage of the infusate in the target putamen. A distance from a posterior end of the target putamen to an anterior end of the target putamen is provided. The distance is along a longitudinal axis of the target putamen. Locations of at least three infusion sites along the longitudinal axis are determined based on the distance. A first of the at least three infusion sites is from 3 mm to 8 mm from the posterior end of the target putamen. A last of the at least three infusion sites is from 5 mm to 15 mm from the anterior end of the target putamen. A remainder of the infusion sites is about equally spaced between the first and last infusion sites. The total infusion volume ($Vi_{(t)}$) of the infusate is provided to be infused into the target putamen. The total infusion volume is greater than 1000 μL. At least three segmental infusion volumes to be independently infused into each of the at least three infusion sites is determined. A sum of the segmental infusion volumes is the total infusion volume ($Vi_{(t)}$). The at least three segmental infusion volumes of the infusate is infused individually into the at least three infusion sites of the target putamen.

[0059] In a further aspect of the above method, the infusing comprises: positioning a distal end of a cannula at the first one of the at least three infusion sites and infusing a first of the at least three segmental infusion volume of the infusate into the first of the at least three infusion sites; advancing the distal end of the cannula to a second of the least three infusion sites and infusing a second of the at least three segmental infusion volumes of the infusate into the second of the at least three infusion sites; and repeating the advancing and the infusing until a last of the at least three segmental infusion volumes of the infusate has been infused into the last of the at least three infusion sites.

[0060] In a further aspect of the above method, the at least three segmental infusion volumes is determined based on a database derived from sample segmental infusion volumes infused into sample infusion sites of sample putamens resulting in sample coverages.

[0061] In a further aspect of the above method, locations of at least three infusion sites are

determined and comprises locations of only a first infusion site, a second infusion site, and a third infusion site. The first infusion site is the first of the least three infusion sites and the third infusion site is the last of the at least three infusion sites. The second infusion site is about midway between the first and the third infusion sites.

[0062] In a further aspect of the above method, the at least three segmental infusion volumes is determined and comprises determining a first segmental infusion volume to be infused into the first infusion site, a second segmental infusion volume to be infused into the second infusion site, and a third segmental infusion volume to be infused into the third infusion site, and wherein the first segmental infusion volume is from about 5% to about 40% of the total infusion volume; the second segmental infusion volume is from about 33% to about 80% of the total infusion volume; and the third segmental infusion volume is from about 7% to about 47% of the total infusion volume.

[0063] In a further aspect of the above method, locations of at least three infusion sites are determined and comprise determining locations of only a first infusion site, a second infusion site, a third infusion site, and a fourth infusion site. The first infusion site is the first of the least three infusion sites and the fourth infusion site is the last of the at least three infusion sites. The second and third infusion sites are about 1/3 and about 2/3 of the distance between the first and fourth infusion sites, respectively.

[0064] In a further aspect of the above method, the at least three segmental infusion volumes are determined and comprise determining a first segmental infusion volume to be infused into the first infusion site, a second segmental infusion volume to be infused into the second infusion site, a third segmental infusion volume to be infused into the third infusion site, and a fourth segmental infusion volume to be infused into the fourth infusion site, and wherein the first segmental infusion volume is from about 2% to about 27% of the total infusion volume; the second segmental infusion volume is from about 20% to about 47% of the total infusion volume; the third segmental infusion volume is from about 20% to about 47% of the total infusion volume; and the fourth segmental infusion volume is from about 7% to about 40% of the total infusion volume.

[0065] In a further aspect of the above method, locations of at least three infusion sites are determined and comprise determining locations of only a first infusion site, a second infusion site, a third infusion site, a fourth infusion site, and a fifth infusion site. The first infusion site is the first of the least three infusion sites and the fifth infusion site is the last of the at least three infusion sites. The second, third, and fourth infusion sites are about 1/4, about 1/2, and about 3/4 of the distance between the first and fifth infusion sites, respectively.

[0066] In a further aspect of the above method, the at least three segmental infusion volumes are determined and comprise determining a first segmental infusion volume to be infused into the first infusion site, a second segmental infusion volume to be infused into the second infusion site, a third segmental infusion volume to be infused into the third infusion site, a fourth segmental infusion volume to be infused into the fourth infusion site, and a fifth segmental infusion volume to be infused into the fifth infusion site, and wherein the first segmental infusion volume is form about 2% to about 27% of the total infusion volume; the second segmental infusion volume is from about 3% to about 23% of the total infusion volume; the third segmental infusion volume is from about 20% to about 47% of the total infusion volume; the fourth segmental infusion volume is from about 10% to about 37% of the total infusion volume; and the fifth segmental infusion volume is from about 3% to about 27% of the total infusion volume.

[0067] In a further aspect of the above method, the therapeutically effective coverage is greater than 40%.

[0068] In yet a further method, a total infusion volume ($Vi_{(t)}$) of an infusate is infused into a target putamen of a subject in need thereof to achieve an infusate coverage of at least 40% in the target putamen. The method comprises verifying the accuracy of the placement of the cannula in the absence of magnetic resonance imaging (MRI). A first segmental infusion volume of the infusate is infused into a first infusion site using a cannula. A distal end of the cannula is advanced to a second infusion site and a second segmental infusion volume of the infusate is infused into the second infusion site. The distal end of the cannula is advanced to a third infusion site and a third segmental infusion volume of the infusate is infused into the third infusion site. The distal end of the cannula is advanced to a fourth infusion site and a fourth segmental infusion volume of the infusate is infused into the fourth infusion site. The second and third infusion sites are located between the first and fourth infusion sites. The aggregate of the first segmental infusion volume, the second segmental infusion volume, the third segmental infusion volume, and the fourth segmental infusion volume is a total infusion volume delivered to the target putamen. The total infusion volume ($Vi_{(T)}$) is greater than 1,000μL. The first segmental infusion volume is from about 2 to about 27% of the total infusion volume and the second segmental infusion volume is from about 20 to about 47% of the total infusion volume. The third segmental infusion volume is from about 20 to about 47% of the total infusion volume, and the fourth segmental infusion volume is from about 7 to about 40% of the total infusion volume.

[0069] In a further aspect of the above method, the infusate coverage by the infusate in the

target putamen is from about 40% to about 90% of a volume of the target putamen of the subject. The infusate coverage by the infusate in the target putamen may be from about 50% to about 80% of the volume of the target putamen of the subject.

[0070] In a further aspect of the above method, the total infusion volume delivered to the target putamen is from about 1,000μL to about 2,000μL. The total infusion volume delivered to the target putamen may be from about 1,200μL to about 1,800μL. The total infusion volume delivered to the target putamen may be from about 1,400μL to about 1,600μL.

[0071] In a further aspect of the above method, the first segmental infusion volume is from about 5 to about 25% of the total infusion volume ($Vi_{(T)}$) and the second segmental infusion volume is from about 20 to about 40% of the total infusion volume. The third segmental infusion volume is from about 20 to about 40% of the total infusion volume, and the fourth segmental infusion volume is from about 10 to about 35% of the total infusion volume such that the percent coverage by the infusate in the target putamen is at least 50% of the volume of the target putamen of the subject.

[0072] In a further aspect of the above method, the first segmental infusion volume is from about 5 to about 25% of the total infusion volume ($Vi_{(T)}$) and the second segmental infusion volume is from about 25 to about 35% of the total infusion volume. The third segmental infusion volume is from about 25 to about 35% of the total infusion volume and the fourth segmental infusion volume is from about 10 to about 30% of the total infusion volume such that the percent coverage by the infusate in the putamen is at least 50% of the volume of the target putamen of the subject.

[0073] In a further aspect of the above method, the first infusion site is located near a posterior end of the target putamen and the fourth infusion site is located near an anterior end of the target putamen. The second infusion site is located approximately equidistance between the first infusion site and the third infusion site. The third infusion site is located approximately equidistance between the second infusion site and the fourth infusion site.

[0074] In a further aspect of the above method, the first infusion site is from about 3 to about 8mm from the posterior end of the target putamen, and the fourth infusion site is from about 5 to about 15mm from the anterior end of the target putamen.

[0075] In a further aspect of the above method, the first segmental infusion volume, the second segmental infusion volume, the third segmental infusion volume, and the fourth segmental infusion volume are infused sequentially.

[0076] In a further aspect of the above method, the cannula comprises a stylet and further including removing the stylet without removing the cannula from the target putamen of the

subject.

[0077] A further aspect of the above method includes measuring the infusate coverage by the infusate in the target putamen after the total infusion volume ($Vi_{(t)}$) of the infusate has been infused.

[0078] In a further aspect of the above method, a rate of the infusate to the target infusion sites of the target putamen is from about 2 to about 12 μL/min.

[0079] The above summary is not intended to represent each embodiment or every aspect of the present disclosure. Rather, the foregoing summary merely provides an example of some of the novel aspects and features set forth herein. The above features and advantages, and other features and advantages of the present disclosure, will be readily apparent from the following detailed description of representative embodiments and modes for carrying out the present invention, when taken in connection with the accompanying drawings and the appended claims. Additional aspects of the disclosure will be apparent to those of ordinary skill in the art in view of the detailed description of various embodiments, which is made with reference to the drawings, a brief description of which is provided below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0080] The disclosure, and its advantages and drawings, will be better understood from the following description of exemplary embodiments together with reference to the accompanying drawings. These drawings depict only exemplary embodiments, and are therefore not to be considered as limitations on the scope of the various embodiments or claims.

[0081] FIG. 1 is a flowchart of infusing an infusate (e.g., a therapeutic infusate) to a target putamen according to one method.

[0082] FIG. 2A is a schematic side view of a putamen with non-anatomical different areas or regions according to one embodiment.

[0083] FIG. 2B is a schematic side view of a cannula according to one embodiment.

[0084] FIG. 2C is a schematic side view of the cannula of FIG. 2B in the putamen of FIG. 2A.

[0085] FIG. 3 is a schematic view of infusing an infusate to a target putamen according to one method.

[0086] FIG. 4 is a flowchart of predicting at least one infusion volume (Vi) of an infusate to a target putamen according to one method.

[0087] FIG. 5 is a table compiling data from eleven subjects (twenty two putamina) including

infusion volumes and putaminal volumes, and putaminal percent coverage.

[0088] FIG. 6 is a chart showing average infusion volumes (Vi) at different distances from the infusion start.

[0089] FIG. 7 is a schematic table that consolidates data from the chart of FIG. 6 and shows various data at different regions or volumes of the target putamen.

[0090] FIG. 8 is a flowchart of determining infusion volume (Vi) according to one method.

[0091] FIG. 9A is a side view of a cannula with two infusion elements according to one embodiment.

[0092] FIG. 9B is a side view of a cannula with two infusion elements according to another embodiment.

[0093] FIG. 9C is a side view of a cannula with two infusion elements according to a further embodiment.

[0094] FIG. 10A is a side view of a cannula with three infusion elements according to one embodiment.

[0095] FIG. 10B is a side view of a cannula with three infusion elements according to another embodiment.

[0096] FIG. 10C is a side view of a cannula with three infusion elements according to a further embodiment.

[0097] FIG. 11A is a side view of a cannula with two infusion elements according to yet a further embodiment.

[0098] FIG. 11B is an enlarged view of the infusion loop in FIG. 11A according to one embodiment.

[0099] FIG. 11C is another side view of the cannula of FIG. 11A.

[0100] FIG. 11D is a side view of a cannula with two infusion elements according to another embodiment.

[0101] FIG. 11E is another side view of the cannula of FIG. 11D.

[0102] FIG. 12A is a side view of a cannula with three infusion elements according to another embodiment.

[0103] FIG. 12B is a side view of a cannula with three infusion elements according to another embodiment.

[0104] FIG. 12C is another side view of the cannula of FIG. 12B.

[0105] FIG. 13A is a side view of a cannula with three infusion elements according to another embodiment.

[0106] FIG. 13B is an enlarged front view of the cannula of FIG. 13A.

[0107] FIG. 13C is another side view of the cannula of FIG. 13A.

[0108] FIG. 14A is a perspective view of a cannula with a removable stylet having a C-shaped cross-section according to one embodiment.

[0109] FIG. 14B is an enlarged perspective view of the cannula of FIG. 14A with broken apart segments.

[0110] FIG. 14C is a cutaway perspective view of the cannula of FIG. 14B.

[0111] FIG. 14D is a cross-sectional view of line 14D-14D in FIG. 14B.

[0112] FIG. 14E is a cross-sectional view of line 14E-14E in FIG. 14B.

[0113] FIG. 14F is an enlarged view of generally circular area 14F in FIG. 14E.

[0114] FIG. 14G is a cross-sectional view of line 14G-14G in FIG. 14B.

[0115] FIG. 14H is a cross-sectional view of line 14H-14H in FIG. 14B.

[0116] FIG. 15A is a view of a cannula assembly according to one embodiment.

[0117] FIG. 15B is an enlarged view of the cannula segments that forms the distal part of the cannula in the cannula assembly of FIG. 15A.

[0118] FIG. 15C is a cross-sectional view of line 15C-15C in FIG. 15A.

[0119] FIG. 15D is a cross-sectional view of line 15D-15D in FIG. 15A.

[0120] FIG. 15E is a cross-sectional view of line 15E-15E in FIG. 15A.

[0121] FIG. 15F is a cross-sectional view of line 15F-15F in FIG. 15A.

[0122] FIG. 15G is an enlarged view of the generally circular area 15G in FIG. 15F.

[0123] FIG. 15H is a cross-sectional view of line 15H-15H in FIG. 15A.

[0124] FIG. 15I is a cross-sectional view of line 15I-15I in FIG. 15A.

[0125] FIG. 16 is a proximal stylet handle according to one embodiment.

[0126] FIG. 17 is a schematic view of a prescriptive infusion approach according to one embodiment.

[0127] FIG. 18 is a schematic view of a prescriptive infusion approach according to another embodiment.

[0128] FIG. 19 is a schematic view of a prescriptive infusion approach according to a further embodiment.

[0129] FIG. 20 is a schematic view of a prescriptive infusion approach according to yet another embodiment.

[0130] FIG. 21 is a schematic view of a prescriptive infusion approach according to another embodiment.

[0131] While the invention is susceptible to various modifications and alternative forms, specific implementations have been shown by way of example in the drawings and will be

described in further detail herein. It should be understood, however, that the invention is not intended to be limited to the particular forms disclosed. Rather, the invention is to cover all modifications, equivalents, and alternatives falling within the spirit and scope of the invention as defined by the appended claims.

DETAILED DESCRIPTION

[0132] Various embodiments are described with reference to the attached figures, where like reference numerals are used throughout the figures to designate similar or equivalent elements. The figures are not drawn to scale and are provided merely to illustrate the instant invention. Several aspects of the invention are described below with reference to example applications for illustration. It should be understood that numerous specific details, relationships, and methods are set forth to provide a full understanding of the invention. One having ordinary skill in the relevant art, however, will readily recognize that the invention can be practiced without one or more of the specific details, or with other methods. In other instances, well-known structures or operations are not shown in detail to avoid obscuring the invention. The various embodiments are not limited by the illustrated ordering of acts or events, as some acts may occur in different orders and/or concurrently with other acts or events. Furthermore, not all illustrated acts or events are required to implement a methodology in accordance with the present invention.

Methods of Infusing and/or Predicting Infusion Volumes

[0133] According to one method, an infusate including a therapeutic agent is infused to a subject. The infusion may occur in the targeted structure (e.g., a brain), for example, and, more specifically, a putamen of a subject. A target putaminal volume of the target putamen is determined. At least one infusion volume (Vi) of the infusate to be infused to at least one of a plurality of target segmental regions of a target putamen is determined. The at least one infusion volume (Vi) is determined by analyzing data (e.g., anatomical, imaging, or other). This data may include: (1) sample putaminal volumes from each sample subject, (2) sample infusion volumes of the infusate for each sample putamen, (3) sample volumes of distribution of the infusate for each sample putamen, and (4) sample percent coverage by the infusate in each sample putamen. The at least one infusion volume of the infusate is infused to the target putamen to achieve a desired percent coverage of the infusate within the targeted structure (e.g., putamen).

[0134] The infusion volume (Vi) is defined as the volume of infusate that is infused to a

target (e.g., a putamen). The infusion volume (Vi) may also be referred to in some embodiments as a therapeutic infusion volume. The term "infusate" is an administrable fluid composition that comprises a therapeutic, an adjuvant for a therapeutic, a biomarker, a buffer, a salt solution, an imaging marker (e.g., contrast agent) or any combinations thereof. Some exemplary infusate compositions include, but are not limited to, compositions comprising viral vectors, non-viral vectors, proteins or peptides, nucleic acids, and/or small molecule chemical compositions. It is contemplated that the insulate may be other administrable fluid compositions.

[0135] In this context, Vi refers to the total infusion volume, which is also specifically referred to as ($Vi_{(T)}$). It is noted that not all of the infusion volume (Vi) may remain in a targeted structure (e.g., a putamen). It is noted that such off-target distribution volume, however, may be acceptable based on the mode of action and toxicity or lack thereof of the therapeutic agent. The volume of distribution (Vd) is defined as the volume of a targeted structure (e.g., a putamen) covered by an infusion volume (Vi). In this context, Vs refers to the total volume of distribution, which is also referred to as $Vd_{(t)}$. The percent coverage is the volume of distribution (Vd) divided by the target volume (e.g., putaminal volume).

[0136] One method of infusing an infusate including a therapeutic agent to a targeted structure (e.g., putamen) is shown in the flowchart of FIG. 1. A putamen comprises two bilaterally symmetrical, oblong, ovular subcortical lobes that extend longitudinally about an anterior-posterior (A-P) axis. As used herein, and as can be determined through context, the term "putamen" can refer to either a single putamen (i.e., the left putamen or right putamen) or both putamen collectively. The putamen are located within the paraventricular deep white matter of the forebrain of each brain hemisphere (telencephalon) and comprise a plurality of nerve cell (neuronal) bodies. The putamen form the striatum together with the adjacent caudate nucleus. The striatum is additionally one component of many that form the basal ganglia of each brain hemisphere. Through various pathways, the putamen are connected to the substantia nigra (including the pars compacta and pars reticulata), the globus pallidus, the claustrum, and the thalamus, in addition to many regions of the cerebral cortex.

[0137] A primary function of the putamen is to regulate the preparation and execution of physical movements and plays a role in various types of learning. The putamen also plays a role in the development of degenerative neurological disorders, such as PD. Retrograde axonal transport of the GDNF protein and/or AAV2 vector from the putamen to substantia nigra is possible; however, anterograde axonal transport of the GDNF protein and/or AAV2 vector to the pars reticulata is more probable in a PD state. The direction of axonal transport

can be determined by the vector used to deliver the GDNF transgene.

[0138] In one embodiment, the rAAV or composition thereof is administered as an infusion via a bi-occipital trajectory. An occipital trajectory is a single posterior trajectory that is substantially parallel to the A-P axis of a putamen and accessed through the occipital bone of a skull. Accordingly, a single burr hole in the occipital bone is needed per putamen. For example, the administration can be performed using the bi-occipital trajectory in which a cannula is guided from the occipital bone using a trajectory that is substantially parallel to the A-P axis of a first putamen and the rAAV is infused while the cannula is being advanced toward a rostral end of the first putamen. The process is then repeated at a second putamen. In a variation, the rAAV is infused into each putamen while the cannula is stationary and not being advanced to the rostral ends of each putamen. FIG. 2C shows an exemplary occipital trajectory.

[0139] Referring to FIG. 1, a step 102 of determining a target putaminal volume of the target putamen is shown. Step 104 determines at least one infusion volume (Vi) to be infused and then step 106 infuses the at least one infusion volume (Vi) to achieve the desired percent coverage. It is contemplated that infusing an infusate including a therapeutic agent to a target putamen may be performed by other methods.

[0140] In one embodiment, an infusate includes a therapeutic agent, a mixing solution, and a magnetic resonance imaging (MRI) contrast agent. The agent is a biologically active compound that is capable of treating at least one disease or condition. In this method, the therapeutic agent is a biologically active compound that is capable of treating at least one disease or condition in the targeted structure (e.g., a putamen). The mixing solution assists in maintaining and keeping the therapeutic agent from potential clumping (e.g., clumping of macromolecules or nanoparticles) and provides more of a consistent and homogenous physiologic mixture. The mixing solution may also assist in providing physiological electrolytes and buffering-pH control to maintain local tissue homoeostasis. The MRI contrast agent provides the ability to monitor the infusion volume (Vi) delivered within the target putamen during, for example, serial MRI scans that are obtained. It is noted that it is not necessary during administration of the infusate with the therapeutic agent to use magnetic resonance imaging (MRI). MRI may be used, however, to assist in guiding a cannula, for example to the targeted structure (e.g., a putamen). It is contemplated that additional components may be added to the infusate.

[0141] Some non-limiting examples of therapeutic agents that may be infused into the target putamen include, but are not limited to, a viral therapeutic, a DNA therapeutic, an RNA

therapeutic, a protein therapeutic, therapeutic nanoparticles, or a small molecule compound.

[0142] Some non-limiting examples of mixing solutions that may be used in the infusate, include, but are not limited to, phosphate buffered saline (PBS) or 180 mM NaCl + 10 mM Na Phosphate + 0.001% Pluronic F68. It is contemplated that other mixing solutions may be used in the infusate.

[0143] Some non-limiting examples of MRI contrast agents that may be used in the infusate include, but are not limited to, gadoteridol (e.g., ProHance®) or gadobutrol (e.g., Gadavist®). It is contemplated that other MRI contrast agents may be used in the infusate.

[0144] A representative example of a target putamen 110 is shown in FIG. 2A according to one embodiment. The putamen is typically a flattened spherical structure that is located near the base of the forebrain of each brain hemisphere of a subject. It is noted, therefore, that there are bilateral putamina in each subject. The method of infusing an infusate into a target putamen occurs in at least one segmental region or volume of the target putamen. The method of infusing an infusate typically occurs in a plurality of segmental regions or volumes of a three-dimensional target putamen. To better describe the segmental regions concept of a target putamen, a representative, two-dimensional target putamen 110 of FIG. 2A has been divided into three arbitrary or theoretical segmental regions or volumes. Thus, these segmental regions or volumes of the target putamen are not actual anatomically divided regions or volumes. Specifically, the target putamen 110 includes a posterior segmental region 112, a middle segmental region 114, and an anterior segmental region 116. The posterior segmental region has the smallest volume, the anterior segmental region has the largest volume, and the middle segmental volume has an area size between the posterior and the anterior segmental regions.

[0145] It is contemplated that a target putamen may be divided into more or less segmental regions or volumes than depicted in the putamen 110 of FIG. 2A. For example, the target putamen may be divided into 2 to 10 or more segmental regions volumes. These segmental regions may correlate with the infusion volumes delivered.

[0146] In one method, at least one infusion volume (Vi) of the infusate is infused to at least one of: (1) the posterior segmental region 112, (2) the middle segmental region 114, and (3) the anterior segmental region 116 of the target putamen 110. In another method, at least one infusion volume (Vi) of the infusate is infused to at least two of: (1) the posterior segmental region 112, (2) the middle segmental region 114, and (3) the anterior segmental region 116 of the target putamen 110. The at least one infusion volume (Vi) of the infusate may be of different infusion volumes to the different segmental regions. In a further method, at least

one infusion volume (Vi) of the infusate is infused in each of: (1) the posterior segmental region 112, (2) the middle segmental region 114, and (3) the anterior segmental region 116 of the target putamen 110. Again, the at least one infusion volume (Vi) of the infusate may be of different infusion volumes in the different segmental regions.

[0147] An example of a cannula 120 in shown in FIG. 2B that is inserted into the target putamen 110 in FIG. 2C. The cannula 120 of FIG. 2B includes a plurality of segments and has a proximal end 122 and a distal end 124. The cannula 120 includes a plurality of ports (not shown) that assists in delivering the infusate to the (1) the posterior segmental region 112, (2) the middle segmental region 114, and (3) the anterior segmental region 116 of the target putamen 110.

[0148] To determine the infusate volume (Vi) to be infused in the target putamen, the putaminal volume is determined before infusion. This is referred to as a target putaminal volume. In one method, the target putaminal volume is determined by at least one magnetic resonance imaging (MRI) scan. In another method, the target putaminal volume is determined by a computerized tomography (CT) scan.

[0149] The infusate volume to be infused is determined by analyzing data in one method. The data to be analyzed may include: (1) sample putaminal volumes from each subject, (2) sample infusion volumes (e.g., segmental infusion volumes) of the infusate for each sample putamen, (3) sample volumes of distribution of the infusate for each sample putamen, and (4) sample percent coverage by the infusate for each sample putamen. It is contemplated that cumulative data may be used and analyzed to assist in determining the optimal infusate volume to be infused, as well as the desired or optimal percent coverage of the putaminal regions.

[0150] The percent coverage is the percentage of the target putaminal volume that is covered by the infusate including the therapeutic agent and acts to influence the target putamen via a therapeutic effect. It is noted that the volume of infusate infused, even though directed to the putamen, may not initially reside or remain in the putamen. Thus, the entire amount of infusate infused is unlikely to remain located in the putamen. It is noted that the percent coverage can be determined for each segmental region and the combined coverage for each region yields the total percent coverage of the putamen. The percent coverage is the volume of distribution (Vd) divided by the target volume (e.g., putaminal volume). The volume of distribution (Vd) of the infusate is determined, for example, in one method by defining the co-infused MRI contrast agent volume within the putamen divided by the target putaminal volume. It is noted that it is not necessary during administration of the infusate with the

therapeutic agent to use magnetic resonance imaging (MRI). MRI may be used, however, to assist in guiding a cannula, for example to the targeted structure (e.g., a putamen).

[0151] The percent coverage by the infusate in one embodiment is typically from about 40% to about 90% of the target putaminal volume. In another embodiment, the percent coverage by the infusate is from about 50% to about 80% of the target putaminal volume. The percent coverage by the infusate in another embodiment is from about 55% to about 75% of the target putaminal volume. The percent coverage by the infusate in a further embodiment is from about 60% to about 75% of the target putaminal volume. The percent coverage by the infusate in yet a further embodiment is from about 60% to about 70% of the target putaminal volume. The percent coverage by the infusate in another embodiment is from about 60% to about 80% of the target putaminal volume.

[0152] As discussed above, the volume of distribution (Vd) is defined as the volume of a target structure (e.g., a putamen) covered by an infusate volume (Vi). The Vd/Vi ratio is a tissue-specific value that is indicative of characteristic infusate distribution within that particular target structure (e.g., the putamen). With respect to the putamen, the Vd/Vi ratio is dependent on a variety of factors including, but not limited to: (1) porosity of the putamen's extracellular space; and (2) the contained amount of white versus gray matter.

[0153] The greater the porosity of the putamen's extracellular space, the lesser the volume of distribution of the infusate, since the infusate distribution will be more readily located and contained within the particular volume containing these porous spaces. In contrast, the greater the quantity of white matter within a targeted structure, the greater the volume of distribution (Vd) of the infusate, since white matter has a very limited extracellular space and thereby promotes infusate distribution toward adjacent extracellular spaces. This, thus, provides a much larger putaminal percent coverage for a given volume of infusion (Vi). In a high porosity example, therefore, the Vd/Vi ratio would be relatively low (e.g., approaching but greater than 1), where in the case of a target structure containing high quantities of white matter, the Vd/Vi ratio would be high (e.g., greater than or equal to about 5). The Vd/Vi ratio ranges for a typical human putamen ranges from about 1.5 to about 3 or more specifically from about 2 to about 3 based on gathered infusion information. In other embodiments, the Vd/Vi ratio ranges from about 1.5 to about 2.5 or from about 2 to about 2.25 for a typical human putamen.

[0154] The infusate including the therapeutic agent may be simultaneously infused into a plurality of regions or segments of the target putamen. In one example, the infusate is simultaneously infused in the target putamen resulting in a: (i) first infusion volume in the

posterior segmental region; (ii) second infusion volume in the middle segmental region; and (iii) third infusion volume in the anterior segmental region. It is contemplated that the infusate may be simultaneously infused in the target putamen into two segmental regions. It is contemplated that the infusate may be simultaneously infused in the target putamen into a plurality of segmental regions ranging from 2 to 10 or more regions. The infused segmental regions of the target putamen are typically from about 3 to about 10 regions. As mentioned above, the segmental regions concept of a target putamen is based on arbitrary or theoretical segmental regions and, thus, are not anatomically divided regions or volumes.

[0155] In one method, infusate is infused into each of a plurality of target segmental regions of a target putamen of a subject in need thereof to achieve a desired percent coverage of the infusate within the target putamen using a system including an interface, a storage device, a processor and an output interface. The processor is coupled to the interface and the storage device and the output interface is coupled to the processor. A target putaminal volume ($Vp_{(t)}$) of the target putamen, a number of target segmental regions of the target putamen, and the desired percent coverage are entered into the interface. The total infusion volume ($Vi_{(t)}$) of the infusate to administer to the target putamen and the segmental infusion volumes to individually administer to each of the plurality of target segmental regions of the target putamen to achieve the desired percent coverage of the infusate are received from the output interface of the system. The segmental infusions volumes of the infusate are infused into each of the plurality of target segmental regions of the target putamen.

[0156] The above method may further include inserting a cannula through a brain of the subject to the target putamen. The cannula includes a flexible body extending from a proximal end to a distal end and the flexible body defines a cannula lumen. A first segmental infusion volume of the infusate is infused into the first segmental region. The distal end of the cannula is advanced to a second segmental region and a second segmental infusion volume of the infusate is infused into the second segmental region. The advancing and infusing steps are repeated until each of the plurality of target segmental regions has been infused with the infusate.

[0157] The above method in another embodiment, includes inserting a cannula through a brain of the subject to the target putamen. The cannula includes a flexible body extending from a proximal end to a distal end. The flexible body defines a cannula lumen. The segmental infusion volumes of the infusate are infused into each of the plurality of target segmental regions of the target putamen in an overlapping manner in which at least a portion of the plurality of target of segmental regions of the target putamen are being infused

simultaneously.

[0158] During the learning process, each segmental region of the sample putamen typically has a different volume. So there is a range of segmental infusion volumes per segmental region. They are all independent and individual. Even if two putamina have the same volume, they may have different volumes injected into each segmental region due to the physiological differences of the putamina (e.g., white v. gray matter, vasculature, etc.). In other words, the spec should describe how multiple segmental infusion volumes corresponding to the same segmental region are considered, e.g., averaged. This strengthens confidence that the amount to be added to target regions is accurate.

[0159] In a target putamen, the at least one infusion volume (Vi) may comprise a first infusion volume ($Vi_{1(t)}$), a second infusion volume ($Vi_{2(t)}$), and a third infusion volume ($Vi_{3(t)}$) that combine to yield a total infusion volume ($Vi_{(T)}$). In one method, the first infusion volume ($Vi_{1(t)}$) is from about 10% to about 30% of the total infusion volume ($Vi_{(T)}$); the second infusion volume ($Vi_{2(t)}$) is from about 30% to about 50% of the total infusion volume ($Vi_{(T)}$); and the third infusion volume ($Vi_{3(t)}$) is from about 30% to about 50% of the total infusion volume ($Vi_{(T)}$). In another method, the first infusion volume ($Vi_{1(t)}$) is from about 15% to about 25% of the total infusion volume ($Vi_{(T)}$); the second infusion volume ($Vi_{2(t)}$) is from about 35% to about 40% of the total infusion volume ($Vi_{(T)}$); and the third infusion volume ($Vi_{3(t)}$) is from about 40% to about 45% of the total infusion volume ($Vi_{(T)}$).

[0160] Referring to FIG. 2A, the above infusion volumes may be correlated to the segmental regions of the target putamen 110. The first infusion volume ($Vi_{1(t)}$) is calculated to be delivered to a posterior segmental region 112 of the target putamen 110, the second infusion volume ($Vi_{2(t)}$) is calculated to be delivered to a middle segmental region 114 of the target putamen 110, and a third infusion volume ($Vi_{3(t)}$) is calculated to be delivered to an anterior segmental region 116 of the target putamen 110.

[0161] FIG. 3 shows a system 200 to determine at least one infusion volume (Vi) of an infusate to be administered to a target putamen 210 of a subject 212. The therapeutic agent may include a viral therapeutic, a DNA therapeutic, an RNA therapeutic, a protein therapeutic, therapeutic nanoparticles, or a small molecule compound. The system 200 in this embodiment includes a magnetic resonance imaging (MRI) device 220. The MRI device 220 provides at least one MRI image of the putamen 210 of the subject 212 for purposes of determining the target putaminal volume of the putamen 210. The resulting MRI images are stored in a storage device or database 222 with data to determine the putaminal volumes of

subjects inclusive of subjects 212. The putaminal volume may be determined from at least one MRI image through techniques such as computer-assisted volumetric analysis or volumetric segmentation analyses. In another system, the putaminal size may be determined from a CT scan using techniques such as computer-assisted volumetric analysis or volumetric segmentation analyses.

[0162] In one embodiment, the storage device or database 222 stores (1) sample putaminal volumes ($Vp_{(s)}$) obtained from sample putamina from a set of sample subjects wherein each sample putamen has a plurality of sample segmental regions; (2) sample infusion volumes ($Vi_{(s)}$) of the infusate infused to each sample segmental region of each sample putamen, wherein a sum of the sample infusion volumes infused into each of the sample segmental regions of each sample putamen is a total sample infusion volume ($Vi_{1(s)} + Vi_{2(s)} \ldots + Vi_{n(s)} = Vi_{T(s)}$); (3) sample volumes of distribution ($Vd_{(s)}$) of the infusate for each sample putamen, the total sample volume of distribution ($Vd_{T(s)}$) being a sum of the sample volumes of distribution ($Vd_{(s)}$), each sample volume of distribution ($Vd_{(s)}$) being a volume of the total sample infusion volume ($Vi_{T(s)}$) retained within each sample putamen; and (4) a sample percent coverage for the infusate in each sample putamen, each sample percent coverage calculated by dividing each sample volume of distribution ($Vd_{(s)}$) by the corresponding sample putaminal volume ($Vp_{(s)}$).

[0163] The system 200 includes an analytic process/controller unit 230 that includes a processor or processing unit 232 that is coupled to the storage device or database 222 via an input interface 234 to receive data on the target putamen and through volumetric software 236 defines and quantifies the target putaminal volume of the putamen 210 of the subject 212. The input interface may receive data on the desired percent overage of the targeted structure (e.g., a putamen). The input interface may receive data on a number of the plurality of target segmental regions of the targeted structure (e.g., a putamen).

[0164] In this example, the processor 232, the volumetric software 236 and delivery-planning software 238 are configured to determine the at least one infusion volume (Vi) based on the target putaminal volume and a desired percent coverage of the target putamen 210 by the infusate. The process in one embodiment also uses a plurality of stored sample data selected from the following: the sample putaminal volumes ($Vp_{(s)}$), a number of sample segmental regions per sample putamen, the sample infusion volumes, the total sample infusion volumes, the sample volumes of distribution, the sample percent coverages, and combinations thereof.

[0165] The processor in a further embodiment may be configured to determine sample volumes of distribution; determine the total sample infusion volume ratio ($Vd_{T(s)}/Vi_{T(s)}$ ratio);

and determine the total infusion volume ($Vi_{(T)}$) of the infusate to administer to the target putamen to achieve the desired percent coverage using the $Vd_{T(s)}/Vi_{T(s)}$ ratio. In another embodiment, a number of plurality of segmental regions of the target structure (e.g., a putamen) may be used by the processor to assist in individually administering the infusion volume (Vi) to each of the target segmental regions of the target putamen to achieve the desired percent coverage of the infusate.

[0166] In one predictive method, a training set is prepared having inputs of the determined sample putaminal volumes, the determined total sample infusion volumes, the determined total sample volumes of distribution, and the determined sample percent coverages. A machine learning model is trained via the training set to predict the total infusion volume of the infusate based on inputs of the target putaminal volume and the desired sample percent coverage of the infusate. In another embodiment, the machine learning model is trained via the training set to predict the infusion volume of the infusate to each of the segmental regions based on inputs of the target putaminal volume and the desired sample percent coverage of the infusate.

[0167] The processor 232 is communicatively coupled to the volumetric software 236 and the delivery-planning software 238. The volumetric software may be obtained from companies such as Brainlab (Munich, Germany). It is contemplated that the volumetric software and the delivery-planning software may be combined together in one software application.

[0168] The processor 232 is coupled to an output interface 239 providing the at least one infusion volume (Vi) in one embodiment. The processor 232 communicates with the output interface 239 to send directions to one or more infusion pumps 244. In another embodiment, the processor may communicate with the output interface to send directions to a plurality of infusion pumps. In another embodiment, the processor 232 is coupled to an output interface providing a rate of infusion signals. The processor 232 is coupled to the output interface 239 and typically provides the at least one infusion volume and a rate of infusion signals, leading to an infusion volume (Vi) to be delivered and providing a theoretical volume of distribution (Vd) within a known targeted structure (e.g., a putamen).

[0169] In one embodiment, the output interface 239 that provides the at least one determined infusion volume (Vi) is coupled to an infusion control system 240. The infusion control system 240 is configured to regulate infusion of the infusate including the therapeutic agent to the target putamen 210. It is contemplated that a plurality of infusion control systems may be used to regulate infusion(s) of the infusate including the therapeutic agent to the target putamen.

[0170] The infusion control system 240 in one embodiment includes a cannula 242, and the infusion pump 244 is operably linked or connected to a one or more reservoirs 246. The reservoir 246 contains the infusate (e.g., a therapeutic infusate). The cannula is operably linked to the reservoir(s) within the infusion pump(s) via the infusion elements that extend through the lumen of the cannula. The reservoir(s) may be a barrel of a syringe in one embodiment. Some non-limiting examples of cannulae will be discussed later in more detail that may be used in the infusion control system 240. It is contemplated that other cannulae may be used in conjunction with the infusion control system 240 to infuse the infusate to the putamen 210. The cannula 242 is inserted into the subject 212 and is positioned to deliver infusate into the putamen 210 in this embodiment.

[0171] The infusion pump 244 delivers infusion volumes of the infusate from the reservoir(s) 246 to the cannula 242 in response to control signals from the processor 232, directed by the delivery-planning software 238. The infusion pump 244 delivers the infusion volume according to a determined infusion rate and total delivered infusion volume as directed by the delivery-planning software 238 from the processor 232. The pump/reservoir may be a syringe pump with the infusate including a therapeutic agent. The syringe pump may be linked to the cannula by suitable means including, but not limited to, a Luer compression fitting and an extended infusion line.

[0172] Some non-limiting pumps that may be used in an infusion control system include, but are not limited to, a screw pump, a piston pump, a syringe pump, or a peristaltic pump. The pump desirably has a constant pressure to deliver a constant volume of infusate over time. It is noted that the pressure may, for example, increase in response to an obstruction so as to keep a constant volume of infusate over time. Some non-limiting examples of commercial pumps that may be used include Medfusion® 3500 or 4000 syringe pumps from Smiths Medical (Minneapolis, MN) and Pefusor® space syringe pump from B. Braun Medical Inc. (Bethlehem, PA).

[0173] It is contemplated that other pumps and/or reservoirs may be used. The pump and reservoir may be combined together in one integral system or may be, for example, separate components that are operably linked with each other through a processor.

[0174] In one system, the infusion control system includes a cannula with multiple ports, a plurality of pumps, and a plurality of reservoirs. In this system, the cannula has a plurality of openings formed therein that allows simultaneous infusion of the infusate in multiple regions or segments of the putamen 210 in the subject 212. A non-limiting example of such multiple regions of a putamen are shown in FIG. 2A, which is described above.

[0175] The system typically includes a separate pump and reservoir for each infusion element of the cannula. Thus, in one method, when the cannula is inserted in the putamen, the infusate is delivered to different regions or segments of the putamen in which each region or segment is supplied by a separate reservoir working in conjunction with a separate pump to deliver the infusate including the therapeutic agent.

[0176] The system 200 further includes a display 250 coupled to the output interface 239 of the analytic process/controller unit 230. The display 250 may display parameters determined by the control routine, such as at least one of the following parameters: infusion volume delivered, current infusion rate, current infusion time, remaining infusion volume to be delivered, remaining infusion time, total infusion volume, and the target putaminal volume. The display 250 may also be configured as a control interface to allow an operator to activate the target volume determination routine, determine the amount of infusate available, and display other data for the subject.

A Method To Predict At Least One Infusion Volume Of An Infusate

[0177] A method to predict at least one infusion volume (Vi) of an infusate including a therapeutic agent to at least one of a plurality of target segmental regions of a target putamen to achieve a desired percent coverage by the infusate within the target putamen includes determining sample putaminal volumes from a set of sample subjects. At least one sample infusion volume of the infusate is infused to at least one of the plurality of sample segmental regions of each sample putamen. A sum of the at least one sample infusion volume for each of the plurality of segmental regions into each sample putamen is a total sample infusion volume.

[0178] A percent coverage for each putamen is chosen from a clinically relevant range. The product of this percent coverage goal and the baseline putaminal volume determined from, for example, MRI (or CT) using analytic software provides a goal volume of distribution (Vd) to attain such coverage. With knowledge of a putamen's Vd/Vi ratio as discussed above, a projected minimum volume of infusion volume (Vi) to achieve that particular volume of distribution (Vd) within the target putamen volume is calculated. The at least one infusion volume (Vi) of the infusate to the at least one of the plurality of segmental regions of each target putamen to achieve the desired volume of distribution (Vd) and percent coverage for the infusate is determined based on the determined target putaminal volume, selected percent putaminal coverage level, and a Vd/Vi ratio, which provide the minimum infusion volume (Vi) to attain such a percent coverage in the particular measured baseline putaminal volume.

[0179] In one method, the processor 232 predicts the infusion volume of the infusate to segmental regions of the target putamen 210 to achieve a desired percent coverage by the infusate within the target putamen 210. Referring to FIG. 4, a flowchart 300 of a predictive computer-implemented method includes step 302 that determines a target putaminal volume. This may be obtained from an MRI (or CT) and compares it to data of sample putaminal volumes from a set of sample subject(s). These data comparisons assist in better understanding the mean subject's putaminal volume compared to the mean and variability (standard deviation or standard error of the mean) for the sample set of target putaminal volumes.

[0180] Step 304 includes accessing data from sample infusion volumes of the infusate to the segmental regions of each sample putamen of the subjects. Each of the sums of the sample infusion volumes for each of the targeted segmental regions is considered a total sample infusion volume. Thus, there is a total sample infusion volume for each of the putamina in a sample set of a subject.

[0181] In step 306, a sample volume of distribution (Vd) for each putamen is estimated from the total sample infusion volume ($Vi_{T(s)}$) for each of the sample subjects, and knowledge of a typical putaminal Vd/ Vi ratio. The product of the total sample infusion volume ($Vi_{T(s)}$) and the Vd/Vi ratio provides an estimated Vd. In step 308, at least one infusion volume (Vi) of the infusate to at least one of the segmental regions of each target putamen for providing the desired percent coverage of the infusate is determined based on the determined target putaminal volume, the infusion of at least one sample infusion volume, a Vd/Vi ratio, and the determined sample volume of distribution (Vd).

[0182] In one embodiment, the volume of distribution (Vd) is determined or measured from MRI scans of the putamen after infusion on each of the sample subjects. In another embodiment, the volume of distribution (Vd) is determined or measured from a CT scan of the putamen after infusion on each of the sample subjects. It is noted that it is not necessary during administration of the infusate with the therapeutic agent to use magnetic resonance imaging (MRI).

[0183] The infusion volume (Vi) of the infusate may be derived from visualizing what the volume of distribution (Vd) looks like, as defined, for example, by using co-infused MRI contrast media with real-time MRI imaging. In another method, the infusion volume (Vi) of the infusate may be derived from visualizing the volume of distribution (Vd) by using a co-infused CT contrast media with real-time CT scanning. The predictive method bases its determination of the predicted volumes of distribution based on the correlations.

[0184] It is desirable to determine the volume of distribution (Vd) for a specific infusion volume (Vi). Once an approximate ratio of Vd/Vi is determined from, for example, specific sample infusions, this allows one to predict the volume of distribution (Vd) for a given infusion volume (Vi). Knowing the predicted volume of distribution (Vd) and the target putaminal volume ($Vp_{(t)}$) also allows one to predict the infusion volume (Vi) to be delivered that will give a specific volume of distribution (Vd) such that the ratio of Vd/Vi will fall in the range of desired putaminal percent coverage.

[0185] Based on the collected data, the infusion volume (Vi) of the infusate to the segmental regions of each target putamen for the desired percent coverage of the infusate may be determined by the predictive method. Specifically, the determination is based on the target putaminal volume (derived from, for example, a baseline MRI of the subject), the sample infusion volume, and an estimated Vd/Vi ratio. The sample volume of distribution (Vd) and precent coverages (derived from, for example, the MRI of a subject after infusion of the infusate), are defined with direct MRI volumetric measurements of the MRI contrast-defined Vd following infusion. Such a measurement of Vd, for a given Vi, allows determination of the actual Vd/Vi ratio for that particular subject, which had only been estimated in advance for the prescriptive calculation. As explained above, the flowchart 300 of the predictive method is based on analyzing infusion test data, and confirming those predictions using actual post-infusion Vd results.

[0186] In addition, the predictive method may be used to determine an infusion rate and an associated infusion time for delivering the at least one infusion volume (Vi) of the infusate to the subject.

[0187] In one method, using DICOM (digital imaging and communications in medicine) data from a recent MRI, a putaminal volumetric segmentation algorithm software (e.g., software from Brainlab AG) defines the putaminal volumes bilaterally in an imaged subject and provides specific baseline right and left putaminal volumes. In this method, the DICOM data is a file set from a set of MRI scans. The putaminal volumes are typically presented in units of cubic centimeters (cm^3) or cubic millimeters (mm^3).

[0188] In an optional step, the target putaminal volumes may be compared with collected sample or historical MRI data to evaluate if any significant volumetric variances are present, compared to the historical sample set. Specifically, the historical putamina and other subcortical brain structures measured using volumetric algorithms, including disease-specific subsets (e.g., Parkinson's disease, multiple system atrophy, or Huntington's disease) may be used to compare subject's volumetric results obtained with age- and disease-matched

historical data sets, to see if significant differences exist from what would be historically anticipated. If there are significant volumetric deviations from historical data, the algorithmically-derived putaminal volume may be redefined (as a check) using a different volume determination method such as, for example, by manual drawing of target volume edges on MRI images and comparing the latter putaminal volume to that determined using the software algorithm.

[0189] Once the target putaminal volume is determined, each putamen's long axis is also measured, to define the infusion distance, from a posterior end (tail) to an anterior end (head) of the putamen, along a likely trajectory for an anticipated cannula passage if using an occipitoparietal burr hole entry point bilaterally. Based on a recent subset of such treated subjects, the mean of a long axis of the putamen was about 37 mm, with a standard deviation of about 2 mm.

[0190] Assuming an occipitoparietal infusion trajectory initiates convection-enhanced delivery (CED) at least 3 mm within the posterior section (tail) of a putamen, and that the most rostral extent of the cannula tip would not advance closer than about 3-4 mm from the most anterior border of the putamen along the same trajectory, the resultant working distance within the putamen measures about 30 mm. Using this working distance (30 mm) for the cannula trajectory within a putamen, recent infusion data showed that 20% of the total infusion volume was delivered within the first 10 mm of each trajectory; from 11 mm to 20 mm of the trajectory, approximately 37% of the infusion volume was distributed; and from 21 mm to 30+ mm of the trajectory, approximately 43% of the infusion volume was delivered based on 11 subjects (22 putamina). This data is shown in FIGS. 5-7, which is discussed detail below.

[0191] Thus, the baseline putaminal volumes, mean putaminal trajectory length, and percent distribution of the total volume of infusate within three hypothetical putaminal volumetric segments have been defined. Based on these parameters, and using a historical estimate of the putaminal Vd/Vi ratio, a prescriptive delivery can be calculated. The putaminal percent coverage is generally from about 40% to about 90% with a mean of about 55-75%. The vector dose is determined by the infusate volume delivered using a single infusate vector concentration. Assuming a total infusion volume (Vi) delivered of 1500 μL (or 1.5 mL), and a vector concentration for our product of 3.3E+12 vector genomes (vg)/mL, a total vector dose delivered to each putamen, therefore, would be 4.95E+12 vg (1.5 mL x 3.3E+12 vg/mL). In such a scenario, the total vector dose received (bilateral putaminal infusions) would be 9.9E+12 vg.

[0192] A Vd/Vi ratio of 2.3 was used based on a historical putaminal mean measure. It is contemplated that other Vd/Vi ratios may be used for putaminal estimates. A subject's actual Vd/Vi ratio is typically determined following CED co-infusions with an MRI contrast agent, and performing volumetric measurements of the putaminal contrast agent visualized. It is noted that it is not necessary during administration of the infusate with the therapeutic agent to use magnetic resonance imaging (MRI). Recent data suggested that with CED of >1500 μL, the Vd/Vi ratio began dropping from about 2.3 toward 0.0 after approximately 1200 μL is delivered, which is believed to be attributed to increasing extra-putaminal leakage.

[0193] In one predictive method, the at least one infusion volume of the infusate is infused. The infusion includes simultaneous infusion of the infusate into multiple regions or segments of a putamen. For example, the regions or segments may be the above-described posterior segmental region 112, the middle segmental region 114 and the anterior segmental region 116 of the target putamen 110 in FIG. 2A. As discussed above, the regions or volumes may differ in number in other methods. This infusion may be accomplished by using a cannula with a plurality of openings formed therein.

[0194] The desired volume of distribution and putaminal percent coverage is typically correlated with a clinical outcome. Thus, the at least one volume of distribution and putaminal percent coverage is verified with a desired clinical outcome using the therapeutic agent in the infusate. Such a correlation may be derived from test data, where the volumes of distribution (Vd) can be verified by, for example, an MRI scan to ensure the desired volumes of distribution (Vd) and percent coverage of the putamen is obtained. The volumes of distribution (Vd) from the test subjects will eventually be correlated to the clinical outcome. The desired clinical outcome following a proposed treatment is identified during clinical trials to mitigate morbidity and mortality, for example, of such central nervous system (CNS) disorders. Some non-limiting examples of CNS disorders include, but are not limiting to, Parkinson's disease (PD), Multiple system atrophy (MSA), Alzheimer's disease (AD), and/or Huntington's disease (HD).

[0195] In one non-limiting example, an infusion volume (Vi) of up to about 1800 μL per putamen is deemed to provide effective treatment for Parkinson's disease, based on the volumes of distribution (Vd) and percent coverage of the putamen provided.

[0196] In one predictive method, three infusion volumes ($Vi_{1(t)}$ range, $Vi_{2(t)}$ range, $Vi_{3(t)}$ range) of an infusate are predicted to be infused into a first target segmental region of the target putamen, a second target segmental region of the target putamen, and a third target segmental region of a target putamen (e.g., putamen 110 of FIG. 2A), respectively. In this method, the

first region is the posterior segmental region, the second region is the middle segmental region, and the third region is the anterior segmental region of the target putamen. The infusion volumes are determined to achieve a desired percent coverage of the infusate of at least about 40% or about 50% of the total target putaminal volume.

[0197] The predictive method determines infusion volumes within sample putamina derived from a set of sample subjects. Each of the putamina of the sample subjects has been arbitrarily divided into three sample segmental regions or volumes to assist in evaluating the distribution of the infusion volumes into each putamen. A first sample infusion volume ($Vi_{1(s)}$) of the infusate is infused to the first sample segmental region of each sample putamen. A second sample infusion volume ($Vi_{2(s)}$) of the infusate is infused to the second sample segmental region of each sample putamen. A third sample infusion volume ($Vi_{3(s)}$) of the infusate is infused to the third sample segmental region of each sample putamen. The sample infusion volumes ($Vi_{1(s)}$, $Vi_{2(s)}$, $Vi_{3(s)}$) combine to yield a total sample infusion volume ($Vi_{T(s)}$) of the infusate. A sample volume of distribution by the infusate in each sample putamen resulting from the total sample infusion volume ($Vi_{T(s)}$) of the infusate is determined. This can be determined, for example, by review of a post-infusion MRI scan of the sample putamen. The sample volume of distribution in one method may be based on visualization using a co-infused MRI contrast agent.

[0198] The relation between the sample infusion volumes $Vi_{1(s)}$, $Vi_{2(s)}$, $Vi_{3(s)}$ and the sample volumes of distribution in the putamina yields is based on the estimated Vd/Vi ratio, and provides the desired percent coverage of the target putamen by the infusate compared to the baseline putaminal volume. In one method, the relation is used in an algorithm for the prediction routine. In this example, the first sample infusion volume $Vi_{1(t)}$ range is from about 10% to about 30% of the total sample infusion volume $Vi_{T(s)}$, the second sample infusion volume $Vi_{2(t)}$ range is from about 30% to about 50% of the total sample infusion volume $Vi_{T(s)}$, and the third sample infusion volume $Vi_{3(t)}$ range is from about 30% to about 50% of the total sample infusion volume $Vi_{T(s)}$.

[0199] In another example, the desired percent coverage of the target putamen by the infusate is from about 40% to about 90%, or from about 50% to about 80% of the target putaminal volume. In a further example, other distributions such as the first sample infusion volume $Vi_{1(t)}$ being from about 15% to about 25% of the total sample infusion volume $Vi_{T(s)}$, the second sample infusion volume $Vi_{2(t)}$ being from about 35% to about 40% of the total sample infusion volume $Vi_{T(s)}$, and the third sample infusion volume $Vi_{3(t)}$ being from about 40% to about 45% of the total sample infusion volume $Vi_{T(s)}$ may be used. In yet another

example, other distributions such as the first sample infusion volume $Vi_{1(t)}$ is about 20% of the total sample infusion volume $Vi_{T(s)}$, the second sample infusion volume $Vi_{2(t)}$ is about 37% of the total sample infusion volume $Vi_{T(s)}$, and the third sample infusion volume $Vi_{3(t)}$ is about 43% of the total sample infusion volume $Vi_{T(s)}$ may be used.

[0200] Referring to FIG. 5, a table 270 of infusion analysis data from 11 subjects and corresponding putamina (each of the subjects had two putamina for a total of 22 putamina) is shown. This data from the 11 subjects was used to derive the prediction method for determining the infusion volume of the infusate into the target putamen. The data from these 22 putamina in FIG. 5 included the overall or total infusion volume ($Vi_{(T)}$) of the infusate, target putaminal volume, and the percent coverage by the infusate contained in the putamina. A mean of the same is shown in FIG. 5.

[0201] The total infusion volume (Vi) of the infusate in FIG. 5 ranged from 955uL to 1800uL with a mean of 1494uL. The target putaminal volume ranged from 3019uL to 4461uL with a mean of 3684uL. The percent coverage by the infusate of the sample putamen ranged from 40% to 81% with a mean percent coverage by the infusate of 63%. The eleven tested subject included those who were at a "mild" disease stage and those who were at a "moderate" disease stage.

[0202] Referring to FIG. 6, a graph 280 is shown with an average infusion volume (Vi) delivered in relation to the infusion trajectory distance from the start of CED co-infusion, including the infusate. The data in FIG. 6 is a combination of data from all 11 subjects' CED infusions into 22 putamina, and therefore, does not relate directly to specific subjects' data shown in FIG. 5. The data presented in FIG. 6 depicts the mean sum of all putaminal infusion volumes delivered within a theoretical subjects' putamen, along a proposed 30+ mm infusion trajectory. When these individual mean volumes at each infusion distance were added together, they provided a denominator for defining the relative volumes delivered in the arbitrary three putaminal segmental volumes, that is the posterior (0-10 mm), middle (11-20 mm) and anterior (21-30+ mm) segmental volumes. The infusion volumes delivered in each segmental volume were added together, and dividing by the total denominator (described above) defined the 20%, 37%, and 43% of total sample infusion volume $Vi_{(t)}$ delivered for each of the three putaminal volumetric regions.

[0203] Referring still to FIG. 6, the average infusion volume (Vi) is shown in uL along the vertical axis, while the distance (in mm) from the infusion start within the long axis of the putamen is shown on the horizontal axis. The areas or regions of the putamen 110 described in FIG. 2A are arbitrarily divided into three regions – posterior segmental region 112, a

middle segmental region 114 and an anterior segmental region 116. A distance of 0-10 mm corresponded to the posterior segmental region of the putamen, a distance of 11-20 mm corresponded to the middle segmental region of the putamen, and a distance of distance 21-30+ mm corresponded to the anterior segmental region. The amount of infusate delivered (Vi) to the anterior segmental region of the putamen was greater than the amount of infusate delivered to the middle segmental region of the putamen. The amount of infusate delivered to the middle segmental region of the putamen was greater than the amount of infusate delivered to the posterior segmental region of the putamen.

[0204] FIG. 7 shows a table 300 derived from the graph 280 of FIG. 6. The data from the eleven test subjects was used to derive the routine for predicting infusion volumes that would be executed by the processor 232, and running the volumetric software 236 and the delivery-planning software 238. The data may also be used to determine maximum infusion volumes of the infusate. The infusion volume (Vi) has a linear relationship with the putaminal volume of distribution (Vd), with a slope that is the Vd/Vi ratio, up to a certain threshold infusion volume and volume of distribution. The putaminal volume of distribution (Vd) determines the putaminal percent coverage, based on the Vd divided by the baseline putaminal volume. Once the threshold infusion volume is reached, further increases in infusion volume typically did not distribute to the same volume of distribution or percent coverage as shown by a reduced Vd/Vi ratio. Thus, the routine also provides theoretical limits to the infusion volume for any given baseline putaminal volume being considered. The data analyses currently predicted that a mean infusion volume (Vi) of 1500 μL will adequately provide >50% putaminal coverage for the majority of putamina undergoing similar infusion volumes and putaminal volumes of distributions with a Vd/Vi ratio of about 2.3.

[0205] Referring still to FIG. 7, a posterior segmental region 312 of the putamen included 20% of the total infusion volume (Vi) of the infusate, while the middle segmental region 314 of the putamen included 37% of the total infusion volume of the infusate, and the anterior segmental region 316 of the putamen included 43% of the total infusion volume of the infusate. Thus, the anterior segmental region 316 had the greatest amount of total infusion volume of the infusate. The regions or volumes of the putamen in FIG. 7 with a distance of 1-10 mm corresponded to the posterior segmental region; a distance of 11-20 mm corresponded with the middle segmental region; and a distance of distance 21-30+ mm corresponded with the anterior segmental region.

[0206] Given an estimated mean total infusion volume of 1500uL, the mean infusion volume of infusate for the posterior segmental region was 300uL (20%) delivered over a mean time

of 65 minutes. The mean infusion volume of infusate for the middle segmental region was 550uL (37%) delivered over a mean time of 38 minutes. The mean infusion volume of infusate for the anterior segmental region was 650uL (43%) delivered over a mean time of 62 minutes.

[0207] As shown in FIG. 7, the number of infusion points for the 11 subjects varied from 2 in the middle segmental region 314, to 3 infusion points in both the posterior segmental region 312 and the anterior segmental region 316. The anterior segmental region 316 had an infusion rate of 10.48 uL/min, the middle segmental region 314 had an infusion rate of 14.47 uL/min, and the posterior segmental region 312 had an infusion rate of 4.6 uL/min. Since the posterior segmental region was the site for initiation of the CED, lower rates were used to promote extracellular distribution, without backflow along the cannula track. Once the cannula was advanced so that the second step was within the posterior border of the putamen, infusion rates were gradually increased to >5-10uL/min.

[0208] The operation of the exemplary system 200 shown in FIG. 3, which may be controlled by the processing unit 232, will now be described with reference to FIG. 8 in conjunction with the flow chart 330. The flow chart 330 of FIG. 8 is representative of machine-readable instructions for implementing an application to determine the infusion volumes for applying an infusate to reach a desired percent coverage within the target putamen. The infusate also needs to have a desired amount or percent of therapeutic agent.

[0209] In this example, the machine-readable instructions comprise an algorithm for execution by: (a) a processor, (b) a controller, and/or (c) one or more other suitable processing device(s). The algorithm may be embodied in software stored on tangible media such as, for example, a flash memory, a CD-ROM, a floppy disk, a hard drive, a digital video (versatile) disk (DVD), or other memory devices, but persons of ordinary skill in the art will readily appreciate that the entire algorithm and/or parts thereof could alternatively be executed by a device other than a processor and/or embodied in firmware or dedicated hardware in a well-known manner (e.g., it may be implemented by an application specific integrated circuit (ASIC), a programmable logic device (PLD), a field programmable logic device (FPLD), a field programmable gate array (FPGA), discrete logic, etc.). For example, any or all of the components of the interfaces could be implemented by software, hardware, and/or firmware. Also, some or all of the machine-readable instructions represented by the flowchart of FIG. 8 may be implemented manually. Further, although the example algorithm is described with reference to the flowchart illustrated in FIG. 8, persons of ordinary skill in the art will readily appreciate that many other methods of implementing the example

machine-readable instructions may alternatively be used. For example, the order of execution of the blocks may be changed, and/or some of the blocks described may be changed, eliminated, or combined.

[0210] Referring to the flow chart 330 of FIG. 8, a target putaminal volume of the putamen is determined from, for example, an MRI image of the putamen in step 332. In step 334, a desired percent coverage by the infusate within the putamen is received from an input in the system. In step 336, a ratio of the volume of distribution (Vd)/volume of infusion (Vi) is provided. This ratio will assist in determining the total infusion volume, which can be subsequently divided into the segmental regions discussed above in some embodiments. In step 338, the total infusion volume is then input into the routine to determine the amount of infusion volume going to each segmental region and may also determine rate(s) of distribution for the infusate. In step 340, the amount of infusion volume going to each segmental region and rate(s) of distribution for the infusate are output to the infusion control system 440.

Cannulae

[0211] The cannulae to be discussed below relate to cannulae for delivering a liquid or material (e.g., an infusion with a therapeutic agent) to a target tissue of an animal, such as brain. More specifically, the cannulae may be used to deliver a liquid or material (e.g., an infusion with a therapeutic agent) to the human brain or other parts of the human central nervous system. The cannulae and their associated infusion systems (i.e., infusion lines, connectors, etc.), enable a practical and leak-resistant connection between a fluid reservoir and the target tissue. The specific design for cannulae discussed below greatly reduce or eliminate reflux (backflow of the infusate material along the cannula) during delivery of the infusate. The cannulae assist in delivering the infusate with minimal reflux along the cannula track and with minimal hold-up volume or dead space.

[0212] The cannulae may be used for convection-enhanced delivery (CED) in one method. In another method, the cannulae may be used for direct injection or other methods of infusion.

[0213] In another embodiment, the cannulae may assist in removing liquid from areas of the body including brain tissue.

[0214] In one embodiment, a cannula configured for fluid delivery includes a body defining a lumen. The body has a proximal end and a distal end. Proximal refers to points closer to the reservoir from which the infusate is dispensed, while distal refers to the points closer to the

point of ultimate delivery of the infusate to the target tissue. The cannula further includes a first infusion element and a second infusion element. The first infusion element is disposed in the lumen and has a first distal end terminating at a first infusion port defined by the body or extending from the distal end of the body. The second infusion element is disposed in the lumen and has a second distal end terminating at a second infusion port defined by the body. The first and second infusion ports are longitudinally spaced from each other, and are typically spaced different distances from the distal end of the body. The cannula is configured such that fluid delivery, through the first and second infusion regions of the cannula, can be independently controlled.

[0215] Referring to FIG. 9A, a cannula 500 is shown that is configured for fluid delivery. In one embodiment, the fluid is an infusate that includes a therapeutic agent. It is contemplated in this embodiment that the infusate to be used in the cannula may further include MRI contrast agents, buffered saline, and specified excipients. The cannula 500 includes a body 502 defining a lumen 504. The body 502 has a proximal end 510 and a distal end 512. In this embodiment, the lumen 504 is an opening (typically a central opening) in the cannula 500. In another embodiment, a lumen may be an opening located between inner and outer walls in a two-walled cannula. The body 502 forms a step 514 located between sections 516a, 516b of the body 502 in which the section 516a has a larger diameter than the section 516b. The sections 516a, 516b are two co-axially disposed segments with each segment having an exterior diameter that defines the exterior diameter of the cannula 500.

[0216] A step in one embodiment is formed by two co-axially disposed segments that different in diameter and include an edge or a substantially vertical edge. A step in another embodiment is formed by two co-axially disposed segments that different in diameter and include an angled transition therebetween. A step in a further embodiment is formed with an integrated segment that is tapered in a manner that increases in diameter.

[0217] The step 514 inhibits or prevents fluid flowing from the infusion port(s) along the cannula from continuing in a lengthwise direction past the step 514 (in the direction of arrow A in FIG. 9A). This reduces reflux (or retrograde passage) of the fluid/material along the cannula. Thus, the step 514 forms a barrier for fluid flow. In one method, the step 514 also assists in determining the distribution shape of a fluid (e.g., an infusate) into a target tissue (e.g., a target putamen).

[0218] The number of steps that are included or formed in a cannula may vary. The step(s) nearest the distal end of the cannula are those that will enter the target tissue first and the number of steps may vary in accordance to the depth of penetration within the target tissue

(e.g., brain). The number of steps may vary also in terms of the location of the port(s) formed in the cannula. Accordingly, the cannula can have from 1 to 10 steps, from 1 to 8 steps, from 1 to 6 steps, from 1 to 4 steps or from 1 to 2 steps. In some embodiments, the cannula has 1 step, 2 steps, 3 steps, 4 steps, 5 steps, 6 steps, 7 steps, 8 steps, 9 steps, or 10 steps.

[0219] In this embodiment, as well as the other cannula embodiments discussed below, the smallest cannula outer diameter (OD) is located at the distal end of the cannula. It is contemplated that the smallest cannula diameter may not be located at the distal end of the cannula, but this would typically not be a desired embodiment.

[0220] The cannula 500 also includes a removable stylet 518. The stylet 518 provides rigidity to the cannula 500 and is removable from within the cannula after assisting in positioning the cannula for delivery of the fluid/material (e.g., an infusate with a therapeutic agent) within the brain target. In various embodiments, after removal of the stylet 518, the cannula is flexible. The removable stylet assists in reinforcing or providing rigidity to the cannula to assist in precisely positioning the cannula for delivery of the fluid/material. The removable stylet assists in determining a straight-line trajectory to properly align the cannula proceeding into the target tissue. In the cannulae described in FIGS. 9A-12C below, it is contemplated that other stylets may be used, including those that are not removable. The stylet 518 has a C-shaped cross section geometry, which allows it to be removed from the cannula after the cannula has been positioned within a tissue of a subject.

[0221] The cannula 500 of FIG. 9A further includes a first infusion element 520 and a second infusion element 530. The first infusion element 520 is disposed in the lumen 504 and has a first distal end 520a terminating at a first infusion port 520b extending from the distal end 512 of the body 502. The length of the first infusion element 520 extending from the distal end 512 of the body 502 may vary. For example, the first infusion element 520 may extend from about 0.5 mm to about 10 mm from the distal end 512 of the body 502. The first infusion element 520 typically extends from about 1 mm to about 5 mm and, more specifically, extends from about 1 mm to about 3 mm from the distal end 512 of the body 502.

[0222] The section 516b has a distal end 524 that acts as a step with the first infusion port 520b extending from the body 502. Thus, the cannula 500 of FIG. 9A is a two-step cannula including the step 514 and the distal end 524.

[0223] It is contemplated that the first infusion port in another embodiment may be defined by the body of the cannula without extending therefrom as shown in FIG. 9A.

[0224] The first and second infusion elements 520, 530 have a generally circular or circular

cross-section. It is contemplated that the first and second infusion elements may have other non-polygonal cross-sectional shapes including oval. It is contemplated that the first and second infusion elements may be of a polygonal cross-sectional shape.

[0225] The infusion elements used in the cannulae typically have a small inner diameter. In one embodiment, the infusion elements have an inner diameter (ID) from about 0.20 mm to about 0.30 mm. In another embodiment, the infusion elements have an inner diameter (ID) from about 0.10 mm to about 0.20 mm. By having an inner diameter that is smaller assists in significantly reducing waste of the fluid due to dead volume within the delivery system. Reduced wastage of product is particularly valuable when the fluid (e.g., infusate) is difficult and/or expensive to obtain. The lower limit of the inner diameter is determined by the resistance provided for fluid flow and any abnormal fluid characteristics generated (e.g., jetting) that would prevent or inhibit safe and efficient bulk flow of the infusate within the extracellular fluid space of the target tissue (e.g., brain).

[0226] The flow rate of the liquid through the infusion elements is generally from about 0.5 to about 30 uL/min. The flow rate of the liquid through the infusion elements in one embodiment is from about 0.5 to about 15 uL/min, and in other embodiments is from about 0.5 to about 5 uL/min, or from about 0.5 to about 10 uL/min.

[0227] The first infusion port 520b is in fluid communication with the first infusion element 520. The first infusion port 520b is an opening or aperture permitting transfer of a liquid outside of the cannula 500. In other words, the first infusion port 520b allows transfer of a fluid (e.g., an infusate) from inside of the cannula 500 to an external environment.

[0228] The second infusion element 530 is disposed in the lumen 504 and has a distal end 530a terminating at an infusion port 502a defined by the body 502. The infusion port 502a is in fluid communication with the second infusion element 530. The infusion port 502a is an opening or aperture formed on a surface of the body 502 and permits transfer of a liquid outside of the cannula 500 from the second infusion element 530. In other words, the infusion port 502a allows transfer of a fluid (e.g., an infusate) from inside of the cannula 500 to an external environment. The first and second infusion ports often are shaped similarly or have the same cross-sectional shape or shapes of respective first and second infusion elements.

[0229] In one non-limiting example, the external environment that may receive the transfer of a fluid (e.g., an infusate) from inside of the cannula is the putamen of the brain, as discussed above. In other embodiments, the external environment may be other locations such as the brain or spinal cord.

[0230] The infusion ports 520b, 502a shown in FIG. 9A are longitudinally spaced from each other. The longitudinal distance is the distance along an axis that extends from a proximal end to a distal end of the cannula. The infusion ports 520b, 502a are also different longitudinal distances from the distal end 512 of the body 504. A longitudinal distance D1 is shown in FIG. 9A between the infusion ports 520b, 502a. In one embodiment, the infusion ports 520b, 502a are longitudinally spaced at least 3 mm from each other. In another embodiment, the infusion ports 520b, 502a are longitudinally spaced at least 5 mm from each other. In a further embodiment, the infusion ports 520b, 502a are longitudinally spaced at least 8 mm from each other. In yet another embodiment, the infusion ports 520b, 502a are longitudinally spaced at least 10 mm from each other.

[0231] The first and second infusion elements 520, 530 in one embodiment may be respective conduits such as shown in the cannula 500 of FIG. 9A. The first infusion element 520 is a first conduit having a first proximal end 520c opposite of the first distal end 520a. The second infusion element 530 is a second conduit having a proximal end 530b opposite to the distal end 530a.

[0232] The first and second infusion elements 520, 530 may be formed from the same or different materials. The first and second infusion elements are typically formed of a material having flexible properties. The first and second infusion elements also are configured to be a low volume line in many embodiments. It is desirable for the first and second infusion elements to conduct the fluid (e.g., infusate) in such a manner where the first and second infusion elements are non-expanding. This assists in conducting the fluid in an efficient manner by minimizing the volume needed, as well as assisting in maintaining the same volume in and out from the infusion elements.

[0233] In one embodiment, the first and second infusion elements 520, 530 are formed from fused silica. It is contemplated that the first and second infusion elements may be formed from other materials such as polyetheretherketone (PEEK) tubing or other non-porous materials.

[0234] The first proximal end 520c of the first infusion element 520 and the proximal end 530b of the second infusion element 530 are in fluidic communication with a fluid (e.g., a therapeutic infusate) contained in a respective reservoir 540a, 540b. One reservoir is typically used with each infusion element. It is contemplated that one reservoir may be used with multiple infusion elements in another embodiment. In one embodiment, the reservoir may be a syringe that holds a desired amount of fluid. It is contemplated that the reservoir may be another component that stores a desired amount of fluid.

[0235] The first and second infusion elements 520, 530 are associated with a first pump 542a and a second pump 542b, respectively. The first and second pumps 542a, 542b are configured to independently effect fluid flow through the first and second infusion elements 520, 530, respectively, from their respective reservoirs 540a, 540b. One pump is typically used with each infusion element. It is contemplated, however, that one pump may be used with multiple infusion elements in another embodiment.

[0236] The fluid is typically delivered from a reservoir (e.g., a syringe) via an infusion line in a desired amount to the infusion element for delivery to a subject. The infusion line is the flexible line from the reservoir (e.g., syringe) to the infusion element in which the fluid travels via a pump. The infusion line is a flexible line that typically has a length of about 5 feet to about 30 feet and, more specifically, from about 10 feet to about 15 feet. A connector (e.g., a Luer fitting) typically is located between the infusion line and the infusion element.

[0237] The cannula 500 is configured such that fluid delivery in first and second infusion regions 522, 532 of the cannula 500 is independently controlled. The first infusion region 522 of FIG. 9A is defined as a general region in which fluid flow occurs from the first infusion port 520b being in fluid communication with the first infusion element 520. It is contemplated that the first infusion region may be defined by a plurality of first infusion ports being in fluid communication with an infusion element(s) in another embodiment. The second infusion region 532 is defined as a general region in which fluid flow occurs from the infusion port 502a with the second infusion element 530.

[0238] The cannula is configured such that at least a portion of the fluid delivery through the first and second infusion regions 522, 532 occurs simultaneously. The fluid delivery in the first and second infusion regions 522, 532 may occur in an overlapping manner such that at least a portion of the fluid delivery through the first and second infusion regions 522, 532 occurs simultaneously.

[0239] It is contemplated that other cannula embodiments may be formed with first and second infusion elements. For example, a cannula may be formed with a second infusion element that is defined by a plurality of second infusion ports.

[0240] Referring to FIG. 9B, a cannula 550 with a body 552 and a lumen 554 is shown that includes the same or similar features as described above in the cannula 500 of FIG. 9A, except that the second infusion element and the number of its infusion ports are different.

[0241] Specifically, the cannula 550 of FIG. 9B includes a second infusion element 560. The second infusion element 560 splits at its distal end into a first end section 560a and a second end section 560b. The body 552 of the cannula 550 forms a first infusion port 552a and a

second infusion port 552b. The first infusion port 552a correlates with the first end section 560a of the second infusion element 560 and is in fluid communication therewith. The second infusion port 552b correlates with the second end section 560b of the second infusion element 560 and is in fluid communication therewith. The first and second infusion ports 552a, 552b function in a similar manner as the infusion port 502a of the cannula 500 discussed above. FIG. 9B also shows the first infusion region 522 (i.e., the region around the first injection port 520b) and a second infusion region 562 (i.e., the region around the first and second infusion ports 552a, 552b).

[0242] A section 516c has a distal end 524 that acts as a step with the first infusion port 520b extending from the distal end 512 of the body 552. Thus, the cannula 550 of FIG. 9B is a two-step cannula including the step 514 and the first distal end 524.

[0243] The cannula 550 and the other cannulae described herein will typically include a reservoir and a pump. These will not be shown for clarity, but would be used in the same manner as the reservoirs 540a, 540b and pumps 542a, 542b of FIG. 9A discussed above. It is noted that an additional reservoir and pump would typically be used in a three infusion-element cannula.

[0244] Referring to FIG. 9C, a cannula according to further embodiment is shown with first and second infusion elements. Specifically, FIG. 9C shows a cannula 570 including a body 572, a lumen 580, a first infusion element 574 and a second infusion element 576. The body 572 includes a proximal end 588 and a distal end 590. The body 502 also includes a first step 594 and a second step 596. The first step 594 is formed between sections 592a, 592b of the body 502 in which the section 592a has a larger diameter than the section 592b. The second step 596 is formed between sections 592b, 592c of the body 502 in which the section 592b has a larger diameter than the section 592c. The cannula 570 is a two-step embodiment.

[0245] The first infusion element 574 splits near its distal end into a first end section 574a and a second end section 574b. The second infusion element 576 splits near its distal end into a first end section 576a and a second end section 576b. The body 572 of the cannula 570 forms a first infusion port 572a, a second infusion port 572b, a third infusion port 572c, and a fourth infusion port 572d.

[0246] The first infusion port 572a correlates with the first end section 574a of the first infusion element 574 and is in fluid communication therewith. The second infusion port 572b correlates with the second end section 574b of the first infusion element 574 and is in fluid communication therewith. The third infusion port 572c correlates with the first section 576a of the second infusion element 576 and is in fluid communication therewith. The fourth

infusion port 572d correlates with the second section 576b of the second infusion element 576 and is in fluid communication therewith. The infusion ports 572a-572d function in the same or similar manner as the infusion ports described above in the cannulae 500, 550. The cannula 570 of FIG. 9C includes a first infusion region 584 (i.e., the region around the first and second infusion ports 572a, 272b) and a second infusion region 586 (i.e., the region around the third and fourth infusion ports 572c, 272d).

[0247] The first and second infusion ports 572a, 572b shown in FIG. 9C are longitudinally spaced from the third and fourth infusion ports 572c, 572d (e.g., different longitudinal distances from the distal end 590 of the body 572). A longitudinal distance D2 is shown in FIG. 9C between the first and second infusion ports 572a, 572b and the third and fourth infusion ports 572c, 572d. In one embodiment, the first and second infusion ports 572a, 572b and the third and fourth infusion ports 572c, 572d are longitudinally spaced at least 3 mm from each other. In another embodiment, the first and second infusion ports 572a, 572b and the third and fourth infusion ports 572c, 572d are longitudinally spaced at least 5 mm from each other. In a further embodiment, the first and second infusion ports 572a, 572b and the third and fourth infusion ports 572c, 572d are longitudinally spaced at least 8 mm from each other. In yet another embodiment, the first and second infusion ports 572a, 572b and the third and fourth infusion ports 572c, 572d are longitudinally spaced at least 10 mm from each other.

[0248] It is contemplated that the cannula may have more than two infusion elements disposed or located in the lumen. For example, the cannula may have three or more infusion elements. Some non-limiting examples of such cannulae are shown in FIGS. 10A-10C.

[0249] Referring to FIG. 10A, a cannula 600 is shown with a body 602 defining a lumen 604. The body 602 has a proximal end 610 and a distal end 612. In this embodiment, the lumen 604 defines an opening (e.g., a central opening) in the cannula 600. In another embodiment, a lumen may be an opening located between inner and outer walls in a two-walled cannula.

[0250] The body 602 of the cannula 600 includes a first step 614a formed between sections 616a, 616b in which the section 616a of the body 602 has a larger diameter than the section 616b. The body 602 includes a second step 614b formed between sections 616b, 616c in which the section 616b of the body 602 has a larger diameter than the section 616c. The first and second steps 614a, 614b assist in inhibiting or preventing fluid flowing from the infusion ports from continuing in a direction past the first and second steps 614a, 614b. The cannula 600 also includes the removable stylet 518.

[0251] The section 616c has a distal end 624 that acts as a step with a first infusion port 620b

extending from the body 602. Thus, the cannula 600 of FIG. 10A is a three-step cannula including steps 614a, 614b and the distal end 624.

[0252] The cannula 600 of FIG. 10A further includes a first infusion element 620, a second infusion element 630, and a third infusion element 640. The first infusion element 620 is disposed in the lumen 604 and has a first distal end 620a terminating at the first infusion port 620b extending from the distal end 612 of the body 602.

[0253] The first infusion port 620b is in fluid communication with the first infusion element 620. The first infusion port 620b is an opening or aperture permitting transfer of a liquid (e.g., therapeutic infusate) outside of the cannula 600 to an external environment.

[0254] The second infusion element 630 is disposed in the lumen 604 and has a distal end 630a terminating at a first infusion port 602a defined by the body 602. The first infusion port 602a is in fluid communication with the second infusion element 630. The first infusion port 602a is an opening or aperture formed on a surface of the body 602 and permits transfer of a liquid outside of the cannula 600 from the second infusion element 630 to an external environment (e.g., a putamen).

[0255] The third infusion element 640 is disposed in the lumen 604 and has a distal end 640a terminating at a second infusion port 602b defined by the body 602. The second infusion port 602b is in fluid communication with the third infusion element 640. The second infusion port 602b is an opening or aperture formed on a surface of the body 602 and permits transfer of a liquid outside of the cannula 600 from the third infusion element 640 to an external environment (e.g., a putamen).

[0256] The infusion ports 620b, 602a, 602b shown in FIG. 10A are longitudinally spaced from each other. A longitudinal distance D3 is shown in FIG. 10A between the infusion ports 620b, 602a, and a longitudinal distance D4 is shown between infusion ports 602a, 602b. In this embodiment, the distance D3 is greater than distance D4. It is contemplated that the distances may the same or may be different than shown in FIG. 10A.

[0257] In one embodiment, the infusion ports 620b, 602a, 602b are longitudinally spaced at least 3 mm from each other. In another embodiment, the infusion ports 620b, 602a, 602b are longitudinally spaced at least 5 mm from each other. In a further embodiment, the infusion ports 620b, 602a, 602b are longitudinally spaced at least 8 mm from each other. In yet another embodiment, the infusion ports 620b, 602a, 602b are longitudinally spaced at least 10 mm from each other.

[0258] The first, second and third infusion elements 620, 630 and 640 in one embodiment may each be a conduit such as shown in FIG. 10A. The first infusion element 620 is a first

conduit having a proximal end 620c opposite of the distal end 620a. The second infusion element 630 is a second conduit having a proximal end 630b opposite of the distal end 630a. The third infusion element 630 is a third conduit having a proximal end 640b opposite of a distal end 640a. The first, second and third infusion elements 620, 630 and 640 may be formed from the same materials as discussed above with the first and second infusion elements 520, 530.

[0259] The cannula 600 is configured such that fluid delivery is independently controlled through the infusion ports 620b, 602a, 602b. The proximal end 620c of the first infusion element 620, the proximal end 630b of the second infusion element 630, and the proximal end 640b of the third infusion element 640 are in fluid communication with a fluid contained in a respective reservoir via respective pumps. The cannula 600 of FIG. 10A includes the first infusion region 642 (i.e., the region around the first infusion port 620a), a second infusion region 644 (i.e., the region around the first infusion port 602a), and a third infusion region 646 (i.e., the region around the second infusion port 602b).

[0260] It is contemplated that other cannulae may be formed with first, second and third infusion elements. Referring to FIG. 10B, a cannula 650 is shown that includes the same or similar features as described above in the cannula 600 of FIG. 10A, except that the second and third infusion elements and the number of infusion ports formed in the body 652 are different. The cannula 650 of FIG. 10B is a three-step cannula.

[0261] Specifically, the cannula 650 of FIG. 10B includes the body 652 and a lumen 654. The cannula 650 further includes the first infusion element 620 (that includes the infusion port 620b), a second infusion element 656 and a third infusion element 662. The second infusion element 656 splits near its distal end into a first end section 656a and a second end section 656b. The third infusion element 662 splits near its distal end into a first end section 662a and a second end section 662b. The body 652 of the cannula 650 forms a first infusion port 652a, a second infusion port 652b, a third infusion port 652c and a fourth infusion port 652d.

[0262] The first infusion port 652a correlates with the first end section 656a of the second infusion element 656 and is in fluid communication therewith. The second infusion port 652b correlates with the second end section 656b of the second infusion element 656 and is in fluid communication therewith. The third infusion port 652c correlates with the first end section 662a of the third infusion element 662 and is in fluid communication therewith. The fourth infusion port 652d correlates with the second end section 662b of the third infusion element 662 and is in fluid communication therewith. The infusion ports 652a-652d function

in a similar manner as discussed above with the infusion ports of the cannulae 500, 600. The cannula 650 of FIG. 10B includes the first infusion region 642 (i.e., the region around the first injection port 620b) a second infusion region 680 (i.e., the region around the first and second infusion ports 652a, 652b), and a third infusion region 682 (i.e., the region around the third and fourth infusion ports 652c, 652d).

[0263] The first infusion port 620b, and the first and second infusion ports 652a, 652b of FIG 10B are longitudinally spaced from each other. The first and second infusion ports 652a, 652b, and the third and fourth infusion ports 652c, 652d of FIG. 10B are longitudinally spaced from each other. The first infusion port 620b, and the third and fourth infusion ports 652c, 652d of FIG 10B are also longitudinally spaced from each other.

[0264] A longitudinal distance D5 is shown in FIG. 10B between the first infusion port 620b and the first and second infusion ports 652a, 652b. A longitudinal distance D6 is shown in FIG. 10B between the first and second infusion ports 652a, 652b, and the third and fourth infusion ports 652c, 652d. Longitudinal distances D5, D6 may be the same as the longitudinal distances D1-D4 discussed above.

[0265] Referring to FIG. 10C, a cannula according to a further embodiment is shown with three infusion elements. Specifically, a cannula 670 of FIG. 10B includes a body 672 and a lumen 674. The cannula 670 is a three-step cannula. The lumen 674 includes a first infusion element 676, a second infusion element 682 and a third infusion element 688. The first infusion element 676 splits near its distal end into a first end section 676a and a second end section 676b. The second infusion element 682 splits near its distal end into a first end section 682a and a second end section 682b. The third infusion element 688 splits at its distal end into a first end section 688a and a second end section 688b. The body 672 of the cannula 670 forms the first infusion port 672a, a second infusion port 672b, a third infusion port 672c, a fourth infusion port 672d, a fifth infusion port 672e, and a sixth infusion port 672f.

[0266] The first infusion port 672a correlates with the first end section 676a of the first infusion element 676 and is in fluid communication therewith. The second infusion port 672b correlates with the second end section 676b of the first infusion element 676 and is in fluid communication therewith. The third infusion port 672c correlates with the first end section 682a of the second infusion element 682 and is in fluid communication therewith. The fourth infusion port 672d correlates with the second end section 682b of the second infusion element 682 and is in fluid communication therewith. The fifth infusion port 672e correlates with the first end section 688a of the third infusion element 688 and is in fluid communication therewith. The sixth infusion port 672f correlates with the second end

section 688b of the third infusion element 688 and is in fluid communication therewith. The cannula 670 of FIG. 10C includes a first infusion region 690 (i.e., the region around the first and second infusion ports 672a, 672b), a second infusion region 692 (i.e., the region around the third and fourth infusion ports 672c, 672d), and a third infusion region 694 (i.e., the region around the fifth and sixth infusion ports 672e, 672f).

[0267] The first and second infusion ports 672a, 672b, and the third and fourth infusion ports 672c, 672d of FIG. 10C are longitudinally spaced from each other. The third and fourth infusion ports 672c, 672d, and the fifth and sixth infusion ports 672e, 672f of FIG. 10C are longitudinally spaced from each other. A longitudinal distance D7 is shown in FIG. 10C between the first and second infusion ports 672a, 672b and the third and fourth infusion ports 672c, 672d. A longitudinal distance D8 of FIG. 10C between the third and fourth infusion ports 672c, 672d and the fifth and sixth infusion ports 672e, 672f. Longitudinal distances D7, D8 may be the same as the longitudinal distances D1-D4 discussed above.

[0268] The cannulae in other embodiments may have infusion elements that terminate into an infusion loop having a plurality of apertures that are aligned or substantially aligned with respective ones of infusion ports formed in a body of a cannula. Some non-limiting examples of the same are shown in FIGS. 11A, 11D, 12A, 12B.

[0269] Referring to FIG. 11A, a cannula 700 is shown being the same or similar to the cannula 500 except that an end of a second infusion element terminates with an infusion loop having a plurality of apertures and the corresponding infusion ports formed in a body of the cannula 700. In one embodiment, each of these plurality of apertures in the infusion loop is aligned or generally aligned with a respective one of a plurality of infusion ports formed in the body of the cannula. The cannula 700 of FIG. 11A includes a body 702, a lumen 704, the first infusion element 520 and a second infusion element 720. The body 702 includes a section 516a and a section 516b in which the section 516a has a larger diameter than the section 516b. The sections 516a, 516b are two co-axially disposed segments with each segment having an exterior diameter that defines the exterior diameter of the cannula 700. The cannula 700 has a proximal end 706 and a distal end 708. The second infusion element 720 is a conduit that has a distal end 720a that terminates with an infusion loop 722. The infusion loop 722 is shown in more detail in FIG. 11B.

[0270] The distal end 708 acts as a step with the first infusion port 520b extending from the body 702. Thus, the cannula 700 of FIG. 11A is a two-step cannula including a step 514 and the distal end 708.

[0271] As shown in FIG. 11B, the infusion loop 722 includes a loop section 722a and

supporting arms 722b, 722c that support the loop section 722a. The loop section 722 is shown in a modified perspective view to better illustrate the details of the loop section 722a, but it is noted that the loop section would typically be in one vertical plane relative to the body. The loop section 722a may be an integrally formed structure or may be connected or joined together with the supporting arms 722b, 722c. The infusion loop is generally circular or circular. It is contemplated that the infusion loop may be of other non-polygonal shapes such as, for example, oval. It is contemplated that the infusion loop may be of a polygonal shape.

[0272] The infusion loop 722 includes a plurality of apertures or opening 724 formed in the loop section 722a. In one embodiment, the plurality of apertures 724 in the infusion loop 722a is aligned or generally aligned with the plurality of infusion ports 726 (see FIG. 11C) formed in the body 702 of the cannula 700. The number of apertures and the number of infusion ports may be the same or may be different. The cannula 700 includes the first infusion region 522 and a second infusion region 728. The cannula 700 functions in a similar method as the cannula 500 described above in transporting fluid (e.g., therapeutic infusate) to an external environment (e.g., a putamen).

[0273] Referring to FIG. 11D, a cannula 730 is shown being the same or similar to the cannula 700 except that each of the ends of the first and second infusion elements terminates with an infusion loop having a plurality of apertures and the corresponding infusion ports formed in a body of the cannula. The cannula 730 of FIG. 11D includes a body 732, a lumen 734, a first infusion element 740 and a second infusion element 750. The cannula has a proximal end 736 and a distal end 738. The cannula 730 is a two-step cannula.

[0274] Both of the first and second infusion elements 740, 750 are conduits that have a respective distal end 740a, 740b that terminates with a respective infusion loop 742, 752. The infusion loops 742, 752 are generally the same as the infusion loop 722 of FIGS. 11A, 11B. The apertures formed in the infusion loop 742 are desirably aligned or substantially aligned with a plurality of infusion ports 744 (see FIG. 11E) formed in the body 732 of the cannula 730. The apertures formed in the infusion loop 752 are desirably aligned or substantially aligned with a plurality of infusion ports 754 (see FIG. 11E) formed in the body 732 of the cannula 730. The cannula 730 includes first and second infusion regions 746, 748. The cannula 730 functions in a similar method as the cannulae 500, 700 described above.

[0275] Referring to FIG. 12A, a cannula 760 is shown. The cannula 760 is the same as the cannula 730 except the infusion element 520 has been added. The cannula 760 includes a plurality of infusion elements 520, 740, 750. The cannula 760 includes the body 732 and the

lumen 734. The body 762 has a plurality of sections 766a, 766b, 766c in which a step 768a is formed between the first and second sections 766a, 766b, and a step 768b is formed between the second and third sections 766b, 766c. The cannula 760 includes the first, second and third infusion regions 522, 746, 748. The cannula 760 functions in a similar method as the cannulae 500, 700, 730 described above.

[0276] The section 766c has a distal end 758 that acts as a step with the first infusion port 520b extending from the body 732. Thus, the cannula 760 of FIG. 12A is a three-step cannula including steps 768a, 768b and the distal end 758.

[0277] Referring to FIG. 12B, a cannula 770 is shown being the same or similar to the cannula 760 except that an additional infusion element terminating with an infusion loop having a plurality of apertures and the corresponding infusion ports formed with an extra body section has been added. In one embodiment, each of these plurality of apertures in the infusion loops is aligned or generally aligned with a respective one of a plurality of infusion ports formed in the body of a cannula.

[0278] The cannula 770 includes a body 772, a lumen 774, the first infusion element 780, a second infusion element 786 and a third infusion element 792. The cannula 770 of FIG. 12B is a three-step cannula. Each of the first, second and third infusion elements 780, 786 and 792 is a conduit that has a respective distal end 780a, 788a, 794a terminating with a respective infusion loop 782, 788, 794. The infusion loops 782, 788, 794 are of different sizes. The infusion loops 782, 788, 794 are similar to the infusion loop 722 of FIG. 11B.

[0279] Each of apertures formed in the infusion loop 782 is desirably aligned or substantially aligned with one or more of a plurality of infusion ports 784 (see FIG. 12C) formed in the body 772 of the cannula 770. Each of apertures formed in the infusion loop 788 is desirably aligned or substantially aligned with one or more of a plurality of infusion ports 790 (see FIG. 12C) formed in the body 772 of the cannula 770. Each of apertures formed in the infusion loop 794 is desirably aligned or substantially aligned with one or more of a plurality of infusion ports 796 (see FIG. 12C) formed in the body 772 of the cannula 770. The cannula 770 includes first, second and third infusion regions 798a-798c, and a plurality of steps 799a-799c.

[0280] It is contemplated that shapes other than a loop may be formed on one or more of the infusion elements to assist in infusing the fluid from the cannula. For example, the loop may be in formed in a hexagonal or octagonal shape.

[0281] In another embodiment, the infusion elements may be different sections of the lumen in a cannula itself. One non-limiting embodiment of the same is shown in FIGS. 13A-13C.

Referring to FIG. 13A, a cannula 800 is shown that includes a body 802. The cannula 800 has a proximal end 804 and a distal end 806. The distal end 806 in the cannula 800 is a closed end. The body 802 forms a first infusion element 820, a second infusion element 826, and a third infusion element 832. The infusion elements 820, 826, 832 are enclosed channels integrated into the cannula 800. The infusion elements 820, 826, 832 are also shown from the proximal end 804 in FIG. 13B. The cannula 800 of FIG. 13A is a three-step cannula (steps 852a-852c)

[0282] Referring to FIGS. 13A, 13C, the fluid (e.g., therapeutic infusate) is configured to be delivered through the infusion elements 820, 826, 832 to respective infusion ports 822, 828, 834 formed in the body 802 of the cannula 800. Each of the infusion elements 820, 826, 832 has a closed end that extends past the respective infusion ports 822, 828, 834.

[0283] In one embodiment, the infusion elements 820, 826, 832 are configured to receive the fluid delivery from a plurality of reservoirs 840a-840c via a respective one of a plurality of conduits 842a-842c with each having a respective adaptor 844a-844c. As discussed above, the reservoirs may be a syringe or other components for storing a desired amount of fluid. The fluid delivery is assisted in one embodiment by having a respective pump for each reservoir. The adaptors 844a-844c assist in accurately placing the respective conduits 842a-842c into the infusion elements 820, 826, 832. The cannula 800 includes a first infusion region 850 (i.e., the region around infusion port 822), a second infusion region 852 (i.e., the region around infusion port 828), and a third infusion region 844 (i.e., the region around infusion port 834).

[0284] Referring to FIGS. 14A-14C, perspective views of a cannula 900 are shown according to another embodiment. To show more detail in certain components of the cannula 900, FIGS. 14B, 14C have been broken apart in four locations I to IV and have been enlarged. Selected individual components have been cut away in FIG. 14C to better illustrate the location of the individualized components with respect to each other. The cannula 900 is continuous from a proximal end 902 to a distal end 904. The cannula 900 assists in fluid delivery of a liquid to a subject. One non-limiting example of a fluid that may be delivered to a subject is an infusate that includes a therapeutic agent. The cannula 900 comprises a tubular inner sleeve 910, a removable rigid stylet 916, a tubular outer sleeve 922, a tip-stylet interface tube 928 (see FIG. 14C), a conical reducer 934, and a step tube 940.

[0285] The stylet 916 provides rigidity to the cannula 900 and is removable from within the cannula after assisting in positioning the cannula for delivery of the fluid/material (e.g., an infusate with a therapeutic agent) within the brain target. In various embodiments, after

removal of the stylet 916, the cannula is flexible.

[0286] Like the cannulae discussed above, the cannula 900 in one embodiment is operably linked to a pump and a reservoir. The pump may be a syringe pump. The cannula 900 is operably linked to a pump and a reservoir via an infusion line that fluidly connects with the tubular inner sleeve 910 that extends through a lumen 912 of the cannula.

[0287] The tubular inner sleeve 910 defines the lumen 912. The lumen 912 extends from a proximal end 910a to a distal end 910b of the tubular inner sleeve 910. The lumen 912 in this embodiment is located in a general center of the cannula 900. The lumen 912 is configured to deliver the fluid to a subject such as, for example, an infusate that includes a therapeutic agent. It is contemplated that the tubular inner sleeve 910 may deliver other fluids. The fluids are delivered from the tubular inner sleeve to an external environment (e.g., a putamen).

[0288] The fluid is typically delivered from a reservoir (e.g., a syringe) via an infusion line in a desired amount to the tubular inner sleeve for delivery to a subject. The infusion line is the flexible line from the reservoir (e.g., syringe) to the tubular inner sleeve in which the fluid travels via a pump. A connector (e.g., a Luer fitting) typically is located between the infusion line and the tubular inner sleeve.

[0289] The tubular inner sleeve may be made from different materials. The tubular inner sleeve may be made from materials such as polyetheretherketone (PEEK), polyimide, fused silica, polyurethane, or combinations thereof. The tubular inner sleeve desirably has some flexibility associated therewith. It is contemplated that the tubular inner sleeve may be of a more flexible/bendable material in one portion (the portion nearer the proximal end 910a) and may be made of a more rigid material (the portion nearer the distal end 910b).

[0290] The tubular inner sleeve has a generally circular or circular cross-section. It is contemplated that the tubular inner sleeve may have other non-polygonal cross-sectional shapes including oval. It is contemplated that the tubular inner sleeve may be of a polygonal cross-sectional shape.

[0291] The tubular inner sleeve 910 in the cannula 900 typically has a small inner diameter. The inner diameter of the tubular inner sleeve is generally from about 0.2 to about 0.25 mm. The outer diameter of the tubular inner sleeve is generally from about 0.30 to 0.45 mm and, more specifically, from about 0.35 to 0.40 mm. A smaller inner diameter of the tubular inner sleeve assists in significantly reducing potential waste of the fluid due to hold-up volume in the delivery system. Reduced wastage of fluid is particularly valuable when the fluid is difficult and/or expensive to obtain. A length L1 of the tubular inner sleeve is generally from

about 120 mm to about 310 mm.

[0292] The flow rate of liquid through the tubular inner sleeve is generally from about 0.5 to about 30 uL/min. The flow rate of the liquid through the tubular inner sleeve in one embodiment is from about 0.5 to about 15 uL/min, and in another embodiment is from about 0.5 to about 5 or 10 uL/min.

[0293] The removable stylet 916 is positioned to surround or partially surround and partially enclose the tubular inner sleeve 910. More particularly, the C-shaped cross-sectional geometry of the stylet 916 allows the stylet 916 to removably receive the tubular inner sleeve 910. The removable stylet 916 assists in providing a rigid, straight line projection to assist in properly aligning the cannula 900 to a pre-planned trajectory proceeding into the target tissue. The removable stylet 916 has a C-shaped cross-sectional geometry. In this embodiment, the C-shaped cross-sectional geometry of the removable stylet 916 remains the same from the onset through removal (if performed). In other words, the C-shaped cross-sectional geometry of the removable stylet 916 is not modified or changed. The removable stylet 916 with its C-shaped cross-sectional geometry is especially desirable because it can be removed from the remainder of the cannula 900 without disconnecting the infusion line directly attached to the tubular inner sleeve 910.

[0294] The removable stylet avoids the methodology of inserting the cannula/typical circular stylet/infusion line within the brain, then removing the typical circular stylet from around the tubular inner sleeve 910 by disconnecting the infusion line, and then reconnecting the infusion line to the tubular inner sleeve 910 of the cannula. Removing a stylet from the remainder of the cannula is especially desirable for longer infusion times (e.g., greater than 24 hours), so as to provide less potential trauma to the brain tissue by making the remainder of the cannula less rigid, e.g., flexible, within the target tissue. The removable stylet is easily removed by a user, without disconnecting the infusion system, so that it is also desirable to remove during shorter infusion times (e.g., less than 24 hours).

[0295] That being said, it is contemplated that the removable stylet may stay with the remainder of the cannula during an infusion, especially for relatively short infusions (less than 12 hours). It is also noted that the removable stylet with a C-shaped cross section geometry is typically assembled with the other cannula components during manufacturing and is received by a user in an assembled state.

[0296] To remove the removable stylet 916 from the remainder of the cannula, the tubular outer sleeve in one embodiment is typically formed with an opening such that the removable stylet can be manually withdrawn without needing to remove or disconnect from the infusion

line. Referring to FIG. 14C, the removable stylet 916 extends concentrically into the tip-stylet interface tube 928 in this embodiment. In another embodiment, a removable stylet may further extend concentrically into a portion of a conical reducer before the conical reducer tapers inwardly.

[0297] The removable stylet may be made from different materials and is straight and rigid. The removable stylet may be made from materials such as, for example, ceramic, zirconia, carbon fiber, or combinations thereof.

[0298] The removable stylet 916 has a proximal end 916a and a distal end 916b. The inner diameter of the removable stylet is generally from about 0.40 mm to about 0.45 mm and the outer diameter of the removable stylet is generally from about 1.30 mm to about 1.35 mm. A length L2 of the removable stylet 916 shown in FIG. 14A is generally from about 225 mm to about 275 mm.

[0299] The step tube 940 extends from a proximal end 940a to a distal end 940b. The step tube 940 is positioned to surround the tubular inner sleeve 910 near the proximal end 910b of the tubular inner sleeve 910 such that a first step 942 is formed between the distal end 940b of the step tube 940 and the tubular inner sleeve 910. The shapes of the step tube 940 and the conical reducer 934 assist in directing or influencing the distribution of liquid flow proximal to the first step.

[0300] In one embodiment, the step tube 940 is attached to the tubular inner sleeve 910 via an adhesive. In this embodiment, the step tube 940 is also attached to the conical reducer 934 via an adhesive. The transition from the conical reducer 934 to the step tube 940 is desirably a smooth transition such that a step is not formed between the two components. In another embodiment, the transition between a conical reducer and a step tube provides a second step, limiting liquid flow along the cannula proximal to the second step.

[0301] The step tube may be made from different materials. It is desired for the step tube to have some rigidity to assist in properly positioning the cannula in the desired location within the target tissue (e.g., brain). The step tube may be made from materials such as polyimides or ceramic.

[0302] The inner diameter of the step tube 940 is generally from about 0.40 mm to about 0.45 mm and the outer diameter of the step tube is generally from about 0.46 mm to about 0.50 mm. It is desirable to have a smaller sized diameter step tube so as to assist in preventing or inhibiting disruption to a target tissue. The larger the diameter of the step tube, the greater the risk of causing disruption to the target tissue. A length L3 of the step tube 940 shown in FIG. 14A is generally from about 5 mm to about 12 mm.

[0303] The tubular outer sleeve 922 extends from a proximal end 922a to the distal end 922b. The tubular outer sleeve 922 surrounds and is spaced from at least a portion of the removable stylet 916. The tubular outer sleeve as shown in FIGS. 14B, 14C extends downwardly towards the distal end 910b and typically covers a portion of the conical reducer 934. The tubular outer sleeve 922 assists in protecting the other components of the cannula 900. The tubular outer sleeve 922 in this embodiment covers the conical reducer 934 until the conical reducer 934 begins to taper inwardly (outer diameter decreases).

[0304] The tubular outer sleeve may be made from different materials. The tubular outer sleeve may be made from materials such as elastomers or polyurethane. One non-limiting example of an elastomer is a Pebax® elastomer.

[0305] The inner diameter of the tubular outer sleeve 922 is generally from about 1.42 mm to about 1.48 mm and the outer diameter of the tubular outer sleeve is from about 1.62 mm to about 1.68 mm. A length L4 of the tubular outer sleeve 922 shown in FIG. 14A is generally from about 250 mm to about 290 mm.

[0306] Referring back to FIG. 14C, a portion of the conical reducer portion 934c in this embodiment is contained within the tubular outer sleeve 922. The conical reducer portion 934 is located adjacent to the step tube 940 and the tip-stylet interface tube 928. The conical reducer 934c may assist in providing a landing zone for the removable stylet 916. The conical reducer 934 is at least partially tapered from a first end 934a to a second end 934b. Thus, an outer diameter of the conical reducer 934 is reduced from the proximal end 934a to the distal end 934b. The proximal end 940a of the step tube 940 and the distal end 934b of the conical reducer 934 form a smooth transition that may provide a second step, based on the change in diameter from the step tube to the conical reducer. The step tube 940 and the conical reducer 934 are attached to each other via an adhesive in one embodiment. An inner surface of the tubular outer sleeve 922 is attached to the outer surface portion 934c of the conical reducer 934 via an adhesive in one embodiment.

[0307] The conical reducer may be made from different materials. It is desired for the conical reducer to have some rigidity to assist in properly positioning the cannula in the desired location within the target tissue (e.g., brain). The conical reducer may be made from materials such as ceramic, alumina or combinations thereof.

[0308] The inner diameter of the conical reducer is generally from about 0.39 mm to about 0.44 mm and the outer diameter of the conical reducer regions is from about 0.7 mm to about 1.47 mm. It is noted that since the outside surface of the conical reducer is tapered, the outer diameter will have both a maximum and a minimum value in each embodiment. A length L5

of the conical reducer 934 of FIG. 14A is generally from about 5.0 mm to about 7.0 mm.

[0309] At least a portion of the tip-stylet interface tube 928 is located concentrically between the removable stylet 916 and the tubular outer sleeve 922. In this embodiment, the tip-stylet interface tube 928 extends to the proximal end 934a of the conical reducer 934. The tip-stylet interface tube 928 assists in providing a landing spot or guide to the removable stylet 916 when inserted into the remainder of the cannula 900, terminating within the proximal segment of the conical reducer 934c. The removable stylet 916 is contained within the tip-stylet interface tube 928. In another embodiment, the tip-stylet interface tube may not extend into a portion of the conical reducer.

[0310] The tip-stylet interface tube may be made from different materials. The tip-stylet interface tube may be made from materials such as polyetheretherketone (PEEK), polyimide, or combinations thereof.

[0311] The inner diameter of the tip-stylet interface tube is generally from about 1.35 mm to about 1.39 mm and the outer diameter of the tip-stylet interface tube is from about 1.41 mm to about 1.45 mm. A length L6 of the tip-stylet interface tube 928 of FIG. 14A is generally from about 275 mm to about 290 mm.

[0312] To better illustrate the relationship and location of the various components of the cannula 900, a number of cross-sectionals of the cannula 900 have been taken from FIG. 14B. FIG. 14D is a cross-sectional view of line 14D-14D in FIG. 14B. FIG. 14D shows a cross-sectional view of the tubular outer sleeve 922, the removable stylet 916 and the tubular inner sleeve 910. FIG. 14E is a cross-sectional view of line 14E-14E in FIG. 14B. FIG. 14E shows a cross-sectional view of the tubular outer sleeve 922, the conical reducer 934 and the tubular inner sleeve 910. FIG. 14F is an enlarged view of the generally circular area in FIG. 14E and includes a cross-sectional view of the tubular outer sleeve 922 and the conical reducer 934.

[0313] FIG. 14G is a cross-sectional view of line 14G-14G in FIG. 14B. FIG. 14G shows a cross-sectional view of the conical reducer 934 and the tubular inner sleeve 910. FIG. 14H is a cross-sectional view of line 14H-14H in FIG. 14B. FIG. 14H shows a cross-sectional view of the step tube 940 and the tubular inner sleeve 910.

[0314] The cannula assembly typically further includes a heat-shrink tube that at least partially covers a remainder of the cannula assembly. The hear-shrink offers protection to the cannula from abrasion and the environment (e.g., moisture, dust). The heat-shrink tube may be made of different materials. Some non-limiting example of materials that may form the heat-shrink tube is polyethylene terephthalate (PET) or paraformaldehyde (PFA).

[0315] The cannula may be used in a method for delivering a fluid to a subject. The method includes providing a cannula (e.g., cannula 900). The cannula is inserted and positioned into the subject. After inserting the cannula in a predetermined position within the subject, the removable stylet is fully withdrawn from the remainder of the cannula. After proper positioning of the cannula, the fluid (e.g., therapeutic infusate) is delivered to the subject through the tubular inner sleeve. The infusion line remains positioned and is not disconnected from the tubular inner sleeve during removal of the removable stylet. Thus, the tubular inner sleeve remains in continuity with the infusate reservoir via the infusion line during the removal of the removable stylet.

[0316] The removable stylet may be removed from the cannula using a number of methods. For example, the removable stylet 916 may be removed in an opening formed in the tubular outer sleeve 922. In this embodiment, it is contemplated that other methods may be used for removing the removable stylet without disconnecting the infusion line or any other component.

[0317] In another method, after inserting and finalizing the position of the cannula, all of the components of the cannula except the removable stylet remain in place after removal of the removable stylet. Thus, in other words, no component of the cannula or cannula assembly needs to be moved or repositioned to remove the removable stylet after the cannula is inserted and positioned.

[0318] Referring to FIG. 15A, a cannula assembly 950 includes a cannula 952, a Y connector 954, a luer fitting 956 and an infusion line 958. A portion of the cannula 952 is shown in FIG. 15B. The infusion line 958 is connected to a reservoir 960 (e.g., a syringe) that receives fluid via a pump 962. Referring to FIGS. 15A, 15B, the cannula 952 includes a tubular inner sleeve 964, a removable stylet 968, a tubular outer sleeve 972, a tip-stylet interface tube 976, a conical reducer 980 and a step tube 984. The cannula 952 functions in a generally similar fashion as the cannula 900 described above.

[0319] The tubular inner sleeve 964 has a proximal end 964a and a distal end 964b as shown best in FIG. 15A. The proximal end 964a of the tubular inner sleeve 964 is located inside of the luer fitting 956. The tubular inner sleeve 964 angles initially downwardly (direction of arrow B) and inwardly (direction of arrow C) through the luer fitting 956 and the Y connector 954 before proceeding only downwardly (direction of arrow B) in the cannula 952. The luer fitting 956 assists in connecting the infusion line 958 and the tubular inner sleeve 964. The step tube 984 functions in the same manner as the step tube 940 and can be made of the same materials and dimensions as discussed above. A step 984a is shown in FIG. 15B between the

step tube 984 and the tubular inner sleeve 964.

[0320] The conical reducer 980 functions in the same manner as conical reducer 934 and can be made of the same materials and dimensions described above. The conical reducer 980 forms a step 980a (FIG 15B) from its tapering. The tip-stylet interface tube 976 functions in the same manner as tip-stylet interface tube 928 described above and can be made of the same materials and dimensions described above.

[0321] The tubular outer sleeve 972 functions in a generally similar manner as the tubular outer sleeve 922 and can be made of the same materials and dimensions described above. The tubular outer sleeve 972 has a proximal end 972a and a distal end 972b. The removable stylet 968 functions in the same manner as the removable stylet 916 and can be made of the same materials and dimensions described above. The removable stylet 968 has a generally C-shaped cross section. The removable stylet has a proximal end 968a and a distal end that is received by at least the tip-stylet interface tube 976. It is also contemplated that in addition to the tip-stylet interface tube, the conical reducer may also assist in forming a landing spot for the removable stylet.

[0322] The Y-connector 954 has a first section 954a and a second section 954b. The first section 954a of the Y-connector 954 surrounds at least a portion of the tubular outer sleeve 972. The second section 954b of the Y-connector 954 receives and protects tubing 988, which surrounds the tubular inner sleeve 964.

[0323] The Y-connector can be made of different materials. Non-limiting examples of materials that may form the Y-connector include, but are not limited to, ceramic, alumina, polyimide, or PEEK. The inner diameter of the Y-connector is generally from about 2.5 to about 3.5 mm and the outer diameter of the Y-connector is from about 5.5 to about 6.5 mm. More specifically, the inner diameter of the Y-connector is generally from about 2.8 to about 3.2 mm and the outer diameter of the Y-connector is from about 5.8 to about 6.2 mm. The Y-connector can be made of different materials.

[0324] The protective tubing 988 assists in protecting the portion of the tubular inner sleeve 964 that extends therethrough. The protective tubing 988 protects the portion of the tubular inner sleeve 964 from abrasion and the environment (e.g., moisture or dust). The protective tubing can be made of different materials. Non-limiting examples of materials that may form the protective tubing include, but are not limited to, Pebax or polyurethane.

[0325] The inner diameter of the protective tubing is generally from about 1.5 to about 1.7 mm and the outer diameter of the protective tubing is from about 3.0 to about 3.3 mm in one embodiment. The inner diameter of the protective tubing is generally from about 1.55 to

about 1.65 and the outer diameter of the protective tubing is from about 3.1 to about 3.2 mm in another embodiment. The outer diameter of the protective tubing 988 is generally about the same as the inner diameter of the Y-connector 954 such that it can be snugly received therein.

[0326] To better illustrate the relationship and location of the various components of the cannula assembly 950, a number of cross-sectionals of the cannula assembly 950 have been taken in FIG. 15A. FIG. 15C is a cross-sectional view of line 15C-15C in FIG. 15A. FIG. 15C shows a cross-sectional view of the removable stylet 968 and the tubular outer sleeve 972. FIG. 15D is a cross-sectional view of line 15D-15D in FIG. 15A. FIG. 15D shows a cross-sectional view of the tubular inner sleeve 964, the removable stylet 968, the tubular outer sleeve 972, and the first section 954a of the Y-connector 954. FIG. 15E is a cross-sectional view of line 15E-15E in FIG. 15A. FIG. 15E shows a cross-sectional view of the tubular inner sleeve 964, the removable stylet 968 and the tubular outer sleeve 972.

[0327] FIG. 15F is a cross-sectional view of line 15F-15F in FIG. 15A. FIG. 15F shows a cross-sectional view of the tubular inner sleeve 964, the removable stylet 968, the tip-stylet interface tube 976 and the tubular outer sleeve 972. The tip-stylet interface tube 976 is directly adjacent to the removable stylet 968. FIG. 15G is an enlarged generally circular area taken from FIG. 15F. FIG. 15H is a cross-sectional view of line 15H-15H in FIG. 15A. FIG. 15H shows a cross-sectional view of the tubular inner sleeve 964 and the conical reducer 980.

[0328] FIG. 15I is a cross-sectional view of line 15I-15I in FIG. 15A. FIG. 15I shows a cross-sectional view of the tubular inner sleeve 964 and the step tube 984.

[0329] The cannulae discussed in this application may be manufactured by different methods. For example, the cannulae may be extruded. It is contemplated that other methods may be used in forming the cannulae.

[0330] To assist in removing the removable stylet from the remainder of the cannula, a separate device from or integrated with the removable stylet may be used. Referring to FIG. 16, a proximal stylet handle 990 with a cannula 992 is shown according to one embodiment. The proximal stylet handle 990 may be attached to or received by the removable stylet to enable easier removal of the removable stylet. It is contemplated that other mechanisms or devices may be used to remove the removable stylet.

[0331] In another method, a total infusion volume ($Vi_{(t)}$) of an infusate is implemented into, infused into, or administered to, a target putamen of a subject in need thereof to achieve a therapeutically effective coverage of the infusate in the target putamen. This method is a prescriptive infusion approach (PIA). The prescriptive infusion approach is desirable because

it eliminates the need to perform intraoperative MR imaging (iMRI) during the infusion of the segmental infusion volumes into the plurality of the infusion sites of the target putamen. The equipment associated with iMRI is costly, and the use of iMRI to monitor an infusion into target putamens of subjects in need thereof consumes a lot of scanner time. Thus, this method can be performed outside of an MRI scanner. The prescriptive infusion approach does not use or require continuous monitoring by iMRI of the infusion into the plurality of infusion sites of the target putamen. Infusate distribution is not monitored or guided in real time via iMRI. In fact, iMRI is not used live or at all during the infusion of the infusate. The need for iMRI therefore limits the availability of such infusions for subjects in need thereof. Thus, many more subjects can be treated using the prescriptive infusion approach without costs associated with expensive equipment.

[0332] This method includes providing a distance from a posterior end of the target putamen to an anterior end of the target putamen. This distance is along a longitudinal axis of the target putamen The locations of a predetermined number of a plurality of infusion sites are determined along the longitudinal axis based on the distance from the posterior end and the anterior end of the target putamen. The method includes providing a total infusion volume ($Vi_{(T)}$) of the infusate to be infused into the target putamen. A plurality of segmental infusion volumes is determined. Each segmental infusion volume of the plurality to be infused into a corresponding infusion site are added up to form a sum of the plurality of segmental infusion volumes being the total infusion volume ($Vi_{(t)}$). These infusion volumes are often different between the target segmental regions. The total infusion volume of the infusate is greater than 500 μL in one embodiment. The total infusion volume of the infusate is typically greater than 1,000 μL. A cannula is inserted and placed through the brain of the subject to the target putamen. Each of the plurality of segmental infusion volumes of the infusate is infused into each of the corresponding plurality of infusion sites of the target putamen.

[0333] The method can be performed, for example, for treating and/or inhibiting the progression of a neurological disorder or disease in the subject (e.g., a human or nonhuman mammal). Thus, as described above, in various aspects the infusate comprises a therapeutic agent and the method achieves therapeutically effective coverage of the infusate in the target putamen. As used herein, the term “therapeutically effective coverage” means a coverage of infusate comprising a therapeutic agent that, when administered to a subject having or suspected of having a neurological disorder, disease or associated condition, is sufficient, either alone or in combination with additional therapies, to effect treatment, such as, for example, by improving at least one symptom of the neurological disorder, disease or

associated condition or inhibiting the progression of the neurological disorder, disease or associated condition. The "therapeutically effective coverage" may vary depending on, for example, the infusate, the therapeutic agent, the condition treated and its severity, and the age and weight of the subject to be or being treated.

[0334] In one embodiment, a therapeutically effective coverage of the infusate is at least 20%. In another embodiment, a therapeutically effective coverage of the infusate is at least 30%. In a further embodiment, a therapeutically effective coverage of the infusate is at least 40%, as discussed in more detail below.

[0335] In one method, the accuracy of the placed cannula is verified using intraoperative computed tomography (iCT). The iCT is used to co-register with, for example, the images previously obtained from MRI. Thus, the cannula may be positioned using preoperative imaging scans and without real-time MRI guidance. Thus, this method may be performed either inside or outside of an operating room (OR), without the need for real-time MRI monitoring. Thus, a portable image guidance system will allow the procedure to occur within a standard OR or in an alternative setting (i.e., outpatient specialized treatment facility) where such portable imaging technologies (e.g., iCT, ultrasound, fluoroscopy, and neuronavigation) can be effectively used for treatment of the individual.

[0336] In another method, the accuracy of the placed cannula is verified using alternative image guidance. Some examples of alternative image guidance include, but are not limited to, ultrasound or fluoroscopy.

[0337] The distance between a posterior end to an anterior end of the putamen along a longitudinal axis is determined prior to using the prescriptive infusion approach. This may be determined by, for example, by preoperative MRI. The prescriptive infusion approach uses a standardized total infusion volume ($Vi_{(T)}$) based on previous clinical experience, which allows sufficient coverage of the target putamen. The distance between the posterior end and the anterior end of the target putamen along a longitudinal axis assists in determining the location of the infusion sites.

[0338] The plurality of infusion sites is at least two infusion sites in this method. The plurality of infusion sites may vary but is generally from about 2 to about 8. In another embodiment, the plurality of infusion sites is from about 3 to about 8. In a further embodiment, the plurality of infusion sites is from about 4 to about 8.

[0339] In one method, a first segmental infusion volume ($Vi_{(1)}$) of the infusate is infused into the first infusion site once a distal end of the cannula has been placed in this first infusion site. The distal end of the cannula is advanced to a second infusion site and a second

segmental infusion volume ($Vi_{(2)}$) of the infusate is infused into the second infusion site. The advancing and infusion steps are repeated until each of the plurality of infusion site has been infused with the infusate. In one specific embodiment, a distal end of the cannula is advanced to a third infusion site and a third segmental infusion volume ($Vi_{(3)}$) of the infusate is infused into the third infusion site. In another embodiment, a distal end of the cannula is advanced to a fourth infusion site and a fourth segmental infusion volume ($Vi_{(4)}$) of the infusate is infused into the fourth infusion site.

[0340] It is contemplated that this may be repeated for additional infusion sites such as fifth, sixth, seventh, eighth, etc. infusion sites wherein a respective segmental infusion volume is infused into each infusion site. The total of each of the segmental infusion volumes infused into a respective infusion site is $Vi_{(T)}$.

[0341] To determine the infusate coverage by the infusate in the target putamen, the volume of the target putamen is needed. The volume of the target putamen may be determined by a preoperative MRI. The infusate coverage by the infusate in the target putamen is determined within about an hour after the total infusion volume has been delivered.

[0342] The infusate is desirably delivered to the target putamen to achieve a therapeutic effective coverage. The infusate coverage by the infusate in the target putamen is from about 20% to about 90% of the volume of the target putamen of the subject in one embodiment. The infusate coverage by the infusate in the target putamen is from about 30% to about 90% of the volume of the target putamen of the subject in another embodiment. The infusate coverage by the infusate in the target putamen is from about 40% to about 90% of the volume of the target putamen of the subject in one embodiment. In another embodiment, the infusate coverage by the infusate in the target putamen is from about 50% to about 90% of the volume of the target putamen of the subject. In a further embodiment, the infusate coverage by the infusate in the target putamen is from about 50% to about 80% of the volume of the target putamen of the subject. In yet another embodiment, the infusate coverage by the infusate in the target putamen is from about 60% to about 80% of the volume of the target putamen of the subject.

[0343] In another embodiment, the infusate coverage by the infusate in the target putamen is from about 40% to about 80% of the volume of the target putamen of the subject. In a further embodiment, the infusate coverage by the infusate in the target putamen is from about 40% to about 70% of the volume of the target putamen of the subject. In yet another embodiment, the infusate coverage by the infusate in the target putamen is from about 40% to about 60% of the volume of the target putamen of the subject.

[0344] In other embodiments, the therapeutically effective coverage is at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 74%, at least 80%, at least 85%, or at least 90%, including coverages of about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79% and about 80% or more.

[0345] The infusing is performed with a syringe pump in one method. Infusing with the syringe pump produces convective delivery of the infusate within the target putamen, which assists in providing safe and effective treatment. It is contemplated that other devices may be used to assist in infusing.

[0346] In one embodiment, the infusion occurs only at the plurality of infusion sites. In other words, the infusion occurs at the infusion sites and there is no infusion when the cannula is being moved between adjacent infusion sites. Thus, the infusions at the infusion sites occur when the cannula is in a stationary state and in a sequential fashion. In another embodiment, infusion continues at the same or at a lower rate while the cannula is moving between adjacent infusion sites. This may be desirable in preventing or inhibiting the plugging of the cannula tip by maintaining the infusion through the cannula at all times, until the infusion is completed at the plurality of infusion sites. In another yet embodiment, the cannula may infuse the infusate to the plurality of infusion sites simultaneously. This may be performed when the cannula is in a stationary state and/or advancing state.

[0347] It is contemplated that the cannulae to be used in the prescriptive infusion approach may include exactly one infusion element that delivers an infusate serially to each of the infusion sites. In another embodiment, the cannula to be used in the prescriptive infusion approach may include a stylet that is removeable from the cannula without removing the cannula from the target putamen of the subject such as the above-described cannula 900 and the cannula 952.

[0348] The cannula to be used in the prescriptive infusion approach may be a cannula

described above. For example, the cannula to be used in the prescriptive infusion approach may be the cannula 500, cannula 550, cannula 570, cannula 600, cannula 650, cannula 670, cannula 700, cannula 730, cannula 760, cannula 770, and cannula 800. Each of these cannulas includes multiple infusion elements.

[0349] It is contemplated that the cannulae to be used in the prescriptive infusion approach may include exactly one infusion element that delivers an infusate to each of the infusion sites in sequence. In another embodiment, the cannula to be used in the prescriptive infusion approach may include a stylet that is removeable from the cannula without removing the cannula from the target putamen of the subject such as the above-described cannula 900 and the cannula 952.

[0350] After the total infusion volume ($Vi_{(t)}$) of the infusate has been delivered, the infusate coverage by the infusate in the target putamen can be measured. The infusate coverage by the infusate in the target putamen after the total infusion volume ($Vi_{(t)}$) of the infusate has been delivered may be measured using MRI. The measurement occurs in one method by removing a stereotactic frame and then moving the patient to a MRI scanner for imaging. This measurement, if performed, will generally occur from about 30 minutes to about 2 or 3 hours after the total infusion volume ($Vi_{(t)}$) of the infusate has been delivered. This measurement, if performed, will typically occur from about 30 minutes to about 1 hour after the total infusion volume ($Vi_{(t)}$) of the infusate has been delivered. Thus, at this point in time of the measurement, there will be an increase in diffusive distribution of infusate beyond the convective distribution at the time when the infusion ends. Therefore, the percent coverages of the infusate determined at a later time will likely be inflated by the diffusion effects. The end-of-infusion percent coverage may be calculated by adjusting for the time after the infusate has been delivered. As discussed above, the infusate coverage is determined within about an hour after the total infusion volume has been delivered.

[0351] The total infusion volume ($Vi_{(T)}$) of the infusate delivered to the target putamen is greater than 500μL in one embodiment. The total infusion volume ($Vi_{(T)}$) of the infusate delivered to the target putamen is greater than 750μL in one embodiment.

[0352] The total infusion volume ($Vi_{(T)}$) of the infusate delivered to the target putamen is greater than 1,000μL in one embodiment. In another embodiment, the total infusion volume of the infusate delivered to the target putamen is greater than 1,200μL. In a further embodiment, the total infusion volume of the infusate delivered to the target putamen is greater than 1,400μL. The total infusion volume of the infusate delivered to the target putamen is generally from about 500 to about 3000 μl, from about 1,000 to about 3,000μL, or

from about 1,000 to about 2,500μL. In other embodiments, the total infusion volume of the infusate delivered to the target putamen is from about 1,000 to about 2,000μL. More specifically, the total infusion volume of the infusate delivered to the target putamen is from about 1,200 to about 2,000 μL, or from about 1,300 to about 1,800 μL. The total infusion volume of the infusate delivered to the target putamen is from about 1,400 to about 1,600 μL in a further embodiment.

[0353] In various aspects, the $Vi_{(T)}$ is about 500 μL, is about 600 μL, is about 700 μL, is about 800 μL, is about 900 μL, is about 1000 μL, about 1050 μL, about 1100 μL, about 1150 μL, about 1200 μL, about 1250 μL, about 1300 μL, about 1350 μL, about 1400 μL, about 1450 μL, about 1500 μL, about 1550 μL, about 1600 μL, about 1650 μL, about 1700 μL, about 1750 μL, about 1800 μL, about 1850 μL, about 1900 μL, about 1950 μL, about 2000 μL, about 2050 μL, about 2100 μL, about 2150 μL, about 2200 μL, about 2250 μL, about 2300 μL, about 2350 μL, about 2400 μL, about 2450 μL, about 2500 μL, about 2550 μL, about 2600 μL, about 2650 μL, about 2700 μL, about 2750 μL, about 2800 μL, about 2850 μL, about 2900 μL, about 2950 μL, or about 3000 μL,

[0354] The infusate, as discussed above, will distribute via convection and diffusion from the infusion sites to locations throughout the putamen. In one non-limiting example using 1,500 μL of infusate, an average putaminal volume delivered was determined at various putaminal trajectory distances. Specifically, at 0mm putaminal trajectory distance (closest to the posterior putaminal border), an average putaminal volume delivered was 62 μL; at 3mm, 31μL was delivered; at 5mm, 106μL was delivered; at 6mm, 6μL was delivered; at 7mm, 3μL was delivered; at 8mm, 56μL was delivered; at 9mm, 15μL was delivered; at 10mm, 60μL was delivered; at 11mm, 2μL was delivered; at 12mm, 48μL was delivered; at 13mm, 144μL was delivered; at 15mm, 146μL was delivered; at 16mm, 48μL was delivered; at 17mm, 18μL was delivered; at 18mm, 160μL was delivered; at 19mm, 23μL was delivered; at 20mm, 72μL was delivered; at 21mm, 75μL was delivered; at 22mm, 63μL was delivered; at 23mm, 23μL was delivered; at 24mm, 53μL was delivered; at 25mm, 21μL was delivered; at 26mm, 152μL was delivered; at 27m, 17μL was delivered; at 28m, 48μL was delivered; at 29mm, 17μL was delivered; at 30mm (closest to the anterior putaminal border), 31μL was delivered.

[0355] The infusate is infused to infusion sites of the target putamen at rates ranging from about 0.5 to about 30 μL/min in one embodiment. The infusate is infused to infusion sites of the target putamen at a rate from about 0.5 to about 20 μL/min in another embodiment. The infusate is infused to infusion sites of the target putamen at a rate from about 0.5 to about 15

μL/min in another embodiment. The infusate is infused to infusion sites of the target putamen at a rate from about 0.5 to about 10 μL/min in a further embodiment.

[0356] The infusate is infused to infusion sites of the target putamen at a rate from about 1 to about 30 μL/min in one embodiment. The infusate is infused to infusion sites of the target putamen at a rate from about 1 to about 20 μL/min in another embodiment. The infusate is infused to infusion sites of the target putamen at a rate from about 1 to about 15 μL/min in a further embodiment. The infusate is infused to infusion sites of the target putamen at a rate from about 1 to about 10 μL/min in a further embodiment.

[0357] The infusate is infused to infusion sites of the target putamen at a rate generally from about 2 to about 20 μL/min in one embodiment. The infusate is infused to infusion sites of the target putamen at a rate generally from about 2 to about 15 μL/min in another embodiment. In a further embodiment, infusate is infused to infusion sites of the target putamen at a rate from about 2 to about 12 μL/min. In a further embodiment, the infusate is infused to infusion sites of the target putamen at a rate from about 2 to about 10 μL/min. In another embodiment, infusate is infused to infusion sites of the target putamen at a rate from about 3 to about 10 μL/min. In yet another embodiment, infusate is infused to infusion sites of the target putamen at a rate from about 3 to about 12 μL/min. In yet another embodiment, infusate is infused to infusion sites of the target putamen at a rate from about 3 to about 15 μL/min. It is contemplated that such higher rates of infusion may be used to deliver the infusate to the plurality of infusion sites of the target putamen.

[0358] In various embodiments, the rate of infusion is about 0.5 μL/min, about 1 μL/min, about 2 μL/min, about 3 μL/min, about 4 μL/min, about 5 μL/min, about 6 μL/min, about 7 μL/min, about 8 μL/min, about 9 μL/min, about 10 μL/min, about 11 μL/min, about 12 μL/min, about 13 μL/min, about 14 μL/min, about 15 μL/min, about 16 μL/min, about 17 μL/min, about 18 μL/min, about 19 μL/min, about 20 μL/min, about 21 μL/min, about 22 μL/min, about 23 μL/min, about 24 μL/min, about 25 μL/min, about 26 μL/min, about 27 μL/min, about 28 μL/min, about 29 μL/min, about 30 μL/min.

[0359] The rates of the infusion may vary between the infusion sites. Typically, the infusate is infused at a lower rate to the first infusion site as compared to the remaining infusion sites. For example, infusate to the first infusion site is typically at a rate not greater than 5 μL/min, while the infusate is infused at higher rates to the remaining infusion sites.

[0360] The rate of infusion should be a minimum amount in some embodiments such that the cannula is not plugged. The rate of infusion also should be of such a level that the size and location of the step or steps of the cannula still assist in reducing or preventing reflux

(backflow) of infusate.

[0361] In one method, the prescriptive infusion approach includes exactly four infusion sites. In this method, the total infusion volume is infused at first, second, third and fourth infusion sites. In this method, the first segmental infusion volume is from about 2 to about 27% of the total infusion volume ($Vi_{(T)}$), the second segmental infusion volume is from about 20 to about 47% of the total infusion volume, the third segmental infusion volume is from about 20 to about 47% of the total infusion volume, and the fourth segmental infusion volume is from about 7 to about 40% of the total infusion volume. The infusate coverage by the infusate in the target putamen is at least 20%, at least 30%, at least 40% of the volume of the target putamen of the subject in one embodiment and at least 50% in another embodiment.

[0362] In another method using exactly four infusion sites, the first segmental infusion volume is from about 5 to about 25% of the total infusion volume ($Vi_{(T)}$), the second segmental infusion volume is from about 20 to about 40% of the total infusion volume, the third segmental infusion volume is from about 20 to about 40% of the total infusion volume, and the fourth segmental infusion volume is from about 10 to about 35% of the total infusion volume. The infusate coverage by the infusate in the target putamen is at least 20%, at least 30%, at least 40% of the volume of the target putamen of the subject in one embodiment and at least 50% in another embodiment.

[0363] In a further method using exactly four infusion sites, the first segmental infusion volume is from about 5 to about 20% of the total infusion volume ($Vi_{(T)}$), the second segmental infusion volume is from about 25 to about 35% of the total infusion volume, the third segmental infusion volume is from about 25 to about 35% of the total infusion volume, and the fourth segmental infusion volume is from about 10 to about 30% of the total infusion volume. The infusate coverage by the infusate in the target putamen is at least 20%, at least 30%, at least 40% of the volume of the target putamen of the subject in one embodiment and at least 50% in another embodiment.

[0364] In yet another method, using exactly four infusion sites, the first segmental infusion volume is from about 25 to about 400µL, and the second segmental infusion volume is from about 300 to 900µL. The third segmental infusion volume is from about 300 to about 900µL, and the second segmental infusion volume is from about 100 to 600µL. The infusate coverage by the infusate in the target putamen in this method is at least 40% of the volume of the target putamen of the subject in one embodiment and at least 50% in another embodiment.

[0365] In another example using exactly four infusion sites, the first segmental infusion

volume is about 10% of the total infusion volume ($Vi_{(T)}$), the second segmental infusion volume is about 33% of the total infusion volume, the third segmental infusion volume is about 33% of the total infusion volume, and the fourth segmental infusion volume is about 23% of the total infusion volume, and the resulting coverage is at least 20%, at least 30%, at least 40%, or at least 50%.

[0366] In one method, the prescriptive infusion approach includes exactly three infusion sites. In this method, the total infusion volume is infused at first, second and third infusion sites. In this embodiment, the first segmental infusion volume is from about 5 to about 40% of the total infusion volume ($Vi_{(T)}$), and the second segmental infusion volume is from about 33 to about 80% of the total infusion volume. The third segmental infusion volume is from about 7 to about 47% of the total infusion volume. The infusate coverage by the infusate in the target putamen is at least 40% of the volume of the target putamen of the subject in one embodiment and at least 50% in another embodiment.

[0367] In another method using exactly three infusion sites, the first segmental infusion volume is from about 5 to about 35% of the total infusion volume ($Vi_{(T)}$), and the second segmental infusion volume is from about 35 to about 70% of the total infusion volume. The third segmental infusion volume is from about 15 to about 45% of the total infusion volume. The infusate coverage by the infusate in the target putamen is at least 40% of the volume of the target putamen of the subject in one embodiment and at least 50% in another embodiment.

[0368] In a further method using exactly three infusion sites, the first segmental infusion volume is from about 5 to about 30% of the total infusion volume ($Vi_{(T)}$), and the second segmental infusion volume is from about 35 to about 60% of the total infusion volume. The third segmental infusion volume is from about 20 to about 40% of the total infusion volume. The infusate coverage by the infusate in the target putamen is at least 40% of the volume of the target putamen of the subject in one embodiment and at least 50% in another embodiment.

[0369] In yet another method, using exactly three infusion sites, the first segmental infusion volume is from about 75 to about 600µL, and the second segmental infusion volume is from about 500 to 1,200µL. The third segmental infusion volume is from about 100 to about 700µL. The infusate coverage by the infusate in the target putamen in this method is at least 40% of the volume of the target putamen of the subject in one embodiment and at least 50% in another embodiment.

[0370] In one method, the prescriptive infusion approach includes exactly five infusion sites.

In this method, the total infusion volume is infused at first, second, third, fourth and fifth infusion sites. In this embodiment, the first segmental infusion volume is from about 2 to about 27% of the total infusion volume ($Vi_{(T)}$), and the second segmental infusion volume is from about 3 to about 30% of the total infusion volume. The third segmental infusion volume is from about 20 to about 63% of the total infusion volume and the fourth segmental infusion volume is from about 7 to about 40% of the total infusion volume. The fifth segmental infusion volume is from about 3 to about 33% of the total infusion volume. The infusate coverage by the infusate in the target putamen is at least 40% of the volume of the target putamen of the subject in one embodiment and at least 50% in another embodiment.

[0371] In another method using exactly five infusion sites, the first segmental infusion volume is from about 5 to about 20% of the total infusion volume ($Vi_{(T)}$), and the second segmental infusion volume is from about 8 to about 25% of the total infusion volume. The third segmental infusion volume is from about 25 to about 55% of the total infusion volume and the fourth segmental infusion volume is from about 10 to about 35% of the total infusion volume. The fifth segmental infusion volume is from about 10 to about 25% of the total infusion volume. The infusate coverage by the infusate in the target putamen is at least 40% of the volume of the target putamen of the subject in one embodiment and at least 50% in another embodiment.

[0372] In a further method using exactly five infusion sites, the first segmental infusion volume is from about 5 to about 15% of the total infusion volume ($Vi_{(T)}$), and the second segmental infusion volume is from about 10 to about 20% of the total infusion volume. The third segmental infusion volume is from about 30 to about 50% of the total infusion volume and the fourth segmental infusion volume is from about 15 to about 30% of the total infusion volume. The fifth segmental infusion volume is from about 10 to about 20% of the total infusion volume. The infusate coverage by the infusate in the target putamen is at least 40% of the volume of the target putamen of the subject in one embodiment and at least 50% in another embodiment.

[0373] In yet another method, using exactly five infusion sites, the first segmental infusion volume is from about 25 to about 400µL, and the second segmental infusion volume is from about 50 to 450µL. The third segmental infusion volume is from about 300 to about 950µL, and the fourth segmental infusion volume is from about 100 to 600µL. The fifth segmental infusion volume is from about 50 to about 500µL. The infusate coverage by the infusate in the target putamen in this method is at least 40% of the volume of the target putamen of the subject in one embodiment and at least 50% in another embodiment.

[0374] In one method, the prescriptive infusion approach includes exactly six infusion sites. In this method, the total infusion volume is infused at first, second, third, fourth, fifth and sixth infusion sites. In this embodiment, the first segmental infusion volume is from about 2 to about 20% of the total infusion volume ($Vi_{(T)}$), and the second segmental infusion volume is from about 2 to about 27% of the total infusion volume. The third segmental infusion volume is from about 7 to about 53% of the total infusion volume and the fourth segmental infusion volume is from about 7 to about 47% of the total infusion volume. The fifth segmental infusion volume is from about 5 to about 37% of the total infusion volume. The sixth segmental infusion volume is from about 2 to about 20% of the total infusion volume. The infusate coverage by the infusate in the target putamen is at least 40% of the volume of the target putamen of the subject in one embodiment and at least 50% in another embodiment.

[0375] In another method using exactly six infusion sites, the first segmental infusion volume is from about 3 to about 18% of the total infusion volume ($Vi_{(T)}$), and the second segmental infusion volume is from about 4 to about 20% of the total infusion volume. The third segmental infusion volume is from about 10 to about 40% of the total infusion volume and the fourth segmental infusion volume is from about 10 to about 40% of the total infusion volume. The fifth segmental infusion volume is from about 10 to about 30% of the total infusion volume. The sixth segmental infusion volume is from about 3 to about 18% of the total infusion volume. The infusate coverage by the infusate in the target putamen is at least 40% of the volume of the target putamen of the subject in one embodiment and at least 50% in another embodiment.

[0376] In a further method using exactly sixth infusion sites, the first segmental infusion volume is from about 5 to about 12% of the total infusion volume ($Vi_{(T)}$), and the second segmental infusion volume is from about 7 to about 15% of the total infusion volume. The third segmental infusion volume is from about 15 to about 30% of the total infusion volume and the fourth segmental infusion volume is from about 15 to about 30% of the total infusion volume. The fifth segmental infusion volume is from about 10 to about 20% of the total infusion volume. The sixth segmental infusion volume is from about 7 to about 15% of the total infusion volume. The infusate coverage by the infusate in the target putamen is at least 40% of the volume of the target putamen of the subject in one embodiment and at least 50% in another embodiment.

[0377] In yet another method, using exactly five infusion sites, the first segmental infusion volume is from about 25 to about 300μL, and the second segmental infusion volume is from

about 25 to 400μL. The third segmental infusion volume is from about 100 to about 800μL, and the fourth segmental infusion volume is from about 100 to 700μL. The fifth segmental infusion volume is from about 75 to about 550μL, and the sixth segmental infusion volume is from about 25 to 300μL. The infusate coverage by the infusate in the target putamen in this method is at least 40% of the volume of the target putamen of the subject in one embodiment and at least 50% in another embodiment.

[0378] The segmental infusion volumes to be infused into different infusion sites are determined independent from each other. Thus, the segmental infusion volumes for each infusion site are individually determined from each other and are not dependent on each other. Each infusion volume corresponds to an infusion at a particular infusion site.

[0379] In one embodiment, various types of information may be entered into an input interface of a system. For example, at least two of the following may be entered into an input interface of the system: the therapeutically effective coverage by the infusate in the target putamen, the total infusion volume ($Vi_{(t)}$), the distance from a posterior end of the target putamen to an anterior end of the target putamen with the distance being along a longitudinal axis of the target putamen, the number of infusion sites of the target putamen, and the rate or rates of the infusate delivered to each of the plurality of infusion sites of the target putamen. The plurality of segmental infusion volumes is determined based on a database derived from sample segmental infusion volumes infused into sample infusion sites of sample putamens resulting in sample coverages.

[0380] Referring to FIG. 17, a non-limiting example of using a prescriptive infusion approach is shown with four infusion sites in a target putamen. As discussed above, the number of infusion sites may be different. Specifically, a cannula 1010 is shown that is configured to be inserted into a putamen 1020 and to deliver infusate at four specific infusion sites 1022, 1024, 1026, 1028 in the putamen 1020. The cannula is, thus, stopped at these four specific infusion sites. The cannula 1010 is a generic cannula that is configured to deliver an infusate to the putamen 1020. Some non-limiting examples of cannulas that may be used include a cannula that includes exactly one infusate opening or the above-described cannulae. The cannula 1010 includes a proximal end 1010a and a distal end 1010b. The cannula 1010 in this embodiment includes at least one infusate opening at or near the distal end 1010b. The cannula 1010 is advanced in the direction of Arrow D from a posterior end 1020a of the putamen 1020 to an anterior end 1020b of the putamen 1020 after an infusion volume has been delivered to each of the infusion sites 1022, 1024, 1026, 1028 as discussed further below.

[0381] The distal end 1010b of the cannula 1010 initially moves to the first infusion site 1022 where it is stopped and a first segmental infusion volume of the infusate is infused therein. The infusate distributes from the first infusion site 1022 generally into a first target segmental region 1030. The distal end 1010b of the cannula 1010 is advanced to the second infusion site 1024 where it is stopped and a second segmental infusion volume of the infusate is infused therein. The infusate distributes from the second infusion site 1024 generally into a second target segmental region 1032. The distal end 1010b of the cannula 1010 is advanced to the third infusion site 1026 where it is stopped and a third segmental infusion volume of the infusate is infused therein. The infusate distributes from the third infusion site 1026 generally into a third target segmental region 1034. The distal end 1010b of the cannula 1010 is advanced to the fourth infusion site 1028 where it is stopped and a fourth segmental infusion volume of the infusate is infused therein. The infusate distributes generally from the fourth infusion site 1028 into a fourth target segmental region 1036. The advancing, stopping, and infusion is repeated until a segmental infusion volume has been infused into each of the infusion sites, whether more or fewer than those depicted in Fig. 17. After a last segmental infusion volume has been infused into a last infusion site at or near the anterior end of the putamen, the cannula can be retracted and removed from the brain and from the subject in its entirety.

[0382] Referring still to FIG. 17, a distance D_9 is shown between the posterior end 1020a and the anterior end 1020b of the putamen 1020 along its longitudinal axis. The distance D_9 is generally from about 30 to about 44 mm, and is typically from about 34 to about 40 mm. The distance D_9 of the putamen 1020 along the longitudinal axis of a subject is measured as discussed above using, for example, MRI. A distance D_{10} is shown between the posterior end 1020a of the putamen 1020 and the first infusion site 1022. The distance D_{10} is generally from about 3 to about 8 mm in one embodiment. In another embodiment, the distance D_{10} is from about 3 to about 6 mm. FIG. 17 also shows a distance D_{11} between the anterior end 1020b of the putamen 1020 and the fourth infusion site 1028. The distance D_{11} is generally from about 5 to about 15 mm in one embodiment. In another embodiment, the distance D_{11} is from about 5 to about 10 mm.

[0383] The second infusion site 1024 and the third infusion site 1026 are located between the first infusion site 1022 and the fourth infusion site 1028. In one embodiment, the second infusion site 1024 and the third infusion site 1026 are about equally separated from each other as well as from the first infusion site 1022 from the second infusion site 1024 and the third infusion site 1026 from the fourth infusion site 1028. Thus, the distances between each

of the adjacent first, second, third and fourth infusion sites 1022, 1024, 1026 and 1028 are the same or about the same in this embodiment. Thus, in FIG. 17, distance D_{12}, distance D_{13} and distance D_{14} may be the same. In another embodiment, the distances D_{12}-D_{14} between each of the adjacent first, second, third and fourth infusion sites 1022, 1024, 1026 and 1028 are the same distance plus or minus 25 percent of each other. In a further embodiment, the distances D_{12}-D_{14} between each of the first, second, third and fourth infusion sites 1022, 1024, 1026 and 1028 are the same percent plus or minus 10 percent of each other.

[0384] The cannula 1010 is configured to infuse a total infusion volume ($Vi_{(T)}$) into the putamen 1020. A first segmental infusion volume $Vi_{(1)}$ eventually distributes into the first target segmental region 1030, a second segmental infusion volume $Vi_{(2)}$ eventually distributes into the second target segmental region 1032, a third segmental infusion volume $Vi_{(3)}$ eventually distributes into the third target segmental region 1034, and a fourth segmental infusion volume $Vi_{(4)}$ eventually distributes into the fourth target segmental region 1036.

[0385] The first segmental infusion volume $Vi_{(1)}$ is generally from about 2 to about 27% of the total infusion volume ($Vi_{(T)}$). The second and third segmental infusion volumes $Vi_{(2)}$, $Vi_{(3)}$ are generally from about 20 to about 60% of the total infusion volume ($Vi_{(T)}$). The fourth segmental infusion volume $Vi_{(4)}$ is generally from about 7 to about 40% of the total infusion volume ($Vi_{(T)}$), The segmental infusion volumes may be infused sequentially or may be infused in two or more infusion sites simultaneously. The infusate coverage by the infusate in the target putamen is at least 20% of the volume of the target putamen of the subject in one embodiment and at least 30% in another embodiment. The infusate coverage by the infusate in the target putamen is at least 40% of the volume of the target putamen of the subject in one embodiment and at least 50% in another embodiment.

[0386] In another embodiment, the first segmental infusion volume is from about 5 to about 25% of the total infusion volume ($Vi_{(T)}$), and the second segmental infusion volume is from about 20 to about 40% of the total infusion volume. The third segmental infusion volume is from about 20 to about 40% of the total infusion volume, and the fourth segmental infusion volume is from about 10 to about 35% of the total infusion volume. The infusate coverage by the infusate in the target putamen is at least 40% of the volume of the target putamen of the subject in one embodiment and at least 50% in another embodiment. The infusate coverage by the infusate in the target putamen is at least 20% of the volume of the target putamen of the subject in one embodiment and at least 30% in another embodiment. The infusate coverage by the infusate in the target putamen is at least 40% of the volume of the target putamen of the subject in one embodiment and at least 50% in another embodiment.

[0387] In a further embodiment, the first segmental infusion volume is from about 5 to about 20% of the total infusion volume, and the second segmental infusion volume is from about 25 to about 35% of the total infusion volume. The third segmental infusion volume is from about 25 to about 35% of the total infusion volume, and the fourth segmental infusion volume is from about 25 to about 35% of the total infusion volume. The infusate coverage by the infusate in the target putamen is at least 20% of the volume of the target putamen of the subject in one embodiment and at least 30% in another embodiment. The infusate coverage by the infusate in the target putamen is at least 40% of the volume of the target putamen of the subject in one embodiment and at least 50% in another embodiment.

[0388] The total infusion volume ($Vi_{(T)}$) of the infusate delivered to the target putamen is greater than or equal to 500μL in one embodiment. The total infusion volume ($Vi_{(T)}$) of the infusate delivered to the target putamen is greater than or equal to 700μL in one embodiment. The total infusion volume ($Vi_{(T)}$) of the infusate delivered to the target putamen is greater than or equal to 900μL in one embodiment.

[0389] The total infusion volume ($Vi_{(T)}$) of the infusate delivered to the target putamen is greater than or equal to 1,000μL in one embodiment. In another embodiment, the total infusion volume of the infusate delivered to the target putamen is greater than or equal to 1,200μL. In a further embodiment, the total infusion volume of the infusate delivered to the target putamen is greater than or equal to 1,400μL. The total infusion volume of the infusate delivered to the target putamen is generally from about 500 to about 3,000μL or, more specifically, from about 1,000 to about 2,500μL or about 3,000μL. In other embodiments, the total infusion volume of the infusate delivered to the target putamen is from about 1,000 to about 2,000μL. More specifically, the total infusion volume of the infusate delivered to the target putamen is from about 1,200 to about 2,000 μL, or from about 1,300 to about 1,800 μL. The total infusion volume of the infusate delivered to the target putamen is from about 1,400 to about 1,600 μL in a further embodiment.

[0390] Referring to FIG. 18, another embodiment of a prescriptive infusion approach is shown that uses a total infusion volume ($Vi_{(T)}$) of about 1,500μL. FIG. 18 shows the cannula 1010 with four infusion sites 1042, 1044, 1046, 1048. The cannula 1010 infuses about 150 μL (about 10% of the total infusion volume) of infusate at the first infusion site 1042. The cannula 1010 infuses about 500 μL (about 33.3% of the total infusion volume) of infusate at both the second and third infusion sites 1044, 1046. The cannula 1010 infuses about 350 μL (about 23.3% of the total infusion volume) of infusate at the fourth infusion site 1048. In this embodiment, the first segmental infusion volume, the second segmental infusion volume, the

third segmental infusion volume, and the fourth segmental infusion volume are infused sequentially.

[0391] The cannula 1010 initially moves to the first infusion site 1042 and infuses a first target segmental infusion volume of the infusate therein and distributes generally into a first segmental region 1050. The distal end 1010b of the cannula 1010 is advanced to a second infusion site 1044 and a second segmental infusion volume of the infusate is infused therein and distributes generally into the second target segmental region 1052. The distal end 1010b of the cannula 1010 is advanced to a third infusion site 1046 and a third segmental infusion volume of the infusate is infused therein and distributes generally into the third target segmental region 1054. The distal end 1010b of the cannula 1010 is advanced to a fourth infusion site 1048 and a fourth segmental infusion volume of the infusate is infused therein and distributes generally into the fourth target segmental region 1056.

[0392] The distance D_9 of FIG. 18 between the posterior end 1020a and the anterior end 1020b of the putamen 1020 along its longitudinal axis. A distance D_{15} is shown between the posterior end 1020a of the putamen 1020 and the first infusion site 1042. The distance D_{15} is generally from about 8-12 mm in one embodiment. FIG 18 also shows a distance D_{16} between the anterior end 1020b of the putamen 1020 and the fourth infusion site 1048. The distance D_{16} is generally from about 6-8 mm.

[0393] The second infusion site 1044 and the third infusion site 1046 are located between the first infusion site 1042 and the fourth infusion site 1048. In one embodiment, the second infusion site 1044 and the third infusion site 1046 are equally separated from each other as well as from the first infusion site 1042 from the second infusion site 1044 and the third infusion site 1046 from the fourth infusion site 1048. This is shown in FIG. 18 with distance D_{17}, distance D_{18} and distance D_{19}. Thus, the distances D_{17}-D_{19} between each of the adjacent first, second, third and fourth infusion sites 1042, 1044, 1046 and 1048 are the same. It is contemplated that distances between adjacent infusion sites may differ from each other.

[0394] Referring to FIG. 19, another embodiment of a prescriptive infusion approach is shown that uses a total infusion volume ($Vi_{(T)}$) of 1,500μL with exactly three infusion sites. FIG. 19 shows the cannula 1010 with three infusion sites 1062, 1064, 1066. The cannula 1010 infuses 300 μL (20% of the total infusion volume) of infusate at the first infusion site 1062 in this embodiment. The cannula 1010 infuses 800 μL (53% of the total infusion volume) of infusate at the second infusion site 1064. The cannula 1010 infuses 400 μL (27% of the total infusion volume) of infusate at the third infusion site 1066. In this embodiment, the first segmental infusion volume, the second segmental infusion volume, and the third

segmental infusion volume are infused sequentially. It is contemplated that the total infusion volumes and amount at each infusion sites may vary such as those embodiments described above.

[0395] The cannula 1010 initially moves to the first infusion site 1062 and infuses a first target segmental infusion volume of the infusate therein and distributes generally into a first segmental region 1068. The distal end 1010b of the cannula 1010 is advanced to the second infusion site 1064 and a second segmental infusion volume of the infusate is infused therein and distributes generally into the second target segmental region 1070. The distal end 1010b of the cannula 1010 is advanced to the third infusion site 1066 and a third segmental infusion volume of the infusate is infused therein and distributes generally into the third target segmental region 1072.

[0396] The distance D_9 is shown in FIG. 19 between the posterior end 1020a and the anterior end 1020b of the putamen 1020 along its longitudinal axis. A distance D_{20} is shown between the posterior end 1020a of the putamen 1020 and the first infusion site 1062. The distance D_{20} is generally from about 6 to about 12 mm in one embodiment. FIG. 19 also shows a distance D_{21} between the anterior end 1020b of the putamen 1020 and the third infusion site 1066. The distance D_{21} is generally from about 6 to about 10 mm.

[0397] The second infusion site 1064 is located between the third infusion site 1066 and the first infusion site 1062. In one embodiment, the second infusion site 1064 is equally separated from the first infusion site 1062 and the third infusion site 1066. This is shown in FIG. 19 with distances D_{22}, D_{23}. Thus, the distances D_{22}, D_{23} between adjacent first, second and third infusion sites 1062, 1064, 1066 are the same. It is contemplated that the distances between adjacent infusion sites may differ from each other.

[0398] Referring to FIG. 20, another embodiment of a prescriptive infusion approach is shown with a total infusion volume ($Vi_{(T)}$) of 1,500μL. FIG. 20 shows the cannula 1010 with five infusion sites 1068, 1070, 1072, 1074, 1076. The cannula 1010 infuses 150 μL (10% of the total infusion volume) of infusate at the first infusion site 1068. The cannula 1010 infuses 200 μL (13% of the total infusion volume) of infusate at the second infusion site 1070. The cannula 1010 infuses 550 μL (37% of the total infusion volume) of infusate at the third infusion site 1072. The cannula 1010 infuses 350 μL (23% of the total infusion volume) of infusate at the fourth infusion site 1074. The cannula 1010 infuses 250 μL (17% of the total infusion volume) of infusate at the fifth infusion site 1076. In this embodiment, the first segmental infusion volume, the second segmental infusion volume, the third segmental infusion volume, the fourth segmental infusion volume and the fifth segmental infusion

volume are infused sequentially. It is contemplated that the total infusion volumes and amount at each infusion sites may vary such as those embodiments described above.

[0399] The cannula 1010 initially moves to the first infusion site 1068 and infuses a first target segmental infusion volume of the infusate therein and distributes generally into a first segmental region 1078. The distal end 1010b of the cannula 1010 is advanced to a second infusion site 1070 and a second segmental infusion volume of the infusate is infused therein and distributes generally into the second target segmental region 1080. The distal end 1010b of the cannula 1010 is advanced to a third infusion site 1072 and a third segmental infusion volume of the infusate is infused therein and distributes generally into the third target segmental region 1082. The distal end 1010b of the cannula 1010 is advanced to a fourth infusion site 1074 and a fourth segmental infusion volume of the infusate is infused therein and distributes generally into the fourth target segmental region 1084. The distal end 1010b of the cannula 1010 is advanced to a fifth infusion site 1076 and a fifth segmental infusion volume of the infusate is infused therein and distributes generally into the fifth target segmental region 1086.

[0400] The distance D_9 is shown in FIG. 20 between the posterior end 1020a and the anterior end 1020b of the putamen 1020 along its longitudinal axis. A distance D_{24} is shown between the posterior end 1020a of the putamen 1020 and the first infusion site 1068. The distance D_{24} is generally from about 5 to about 10 mm in one embodiment. FIG 20 also shows a distance D_{25} between the anterior end 1020b of the putamen 1020 and the fifth infusion site 1076. The distance D_{25} is generally from about 6 to about 8 mm.

[0401] The second infusion site 1070, the third infusion site 1072 and the fourth infusion site 1074 are located between the first infusion site 1068 and the fifth infusion site 1076. In one embodiment, each of the adjacent infusion sites (the first infusion site 1068, the second infusion site 1070, the third infusion site 1072, the fourth infusion site 1074 and the fifth infusion site 1076) are equally separated from each other as well. Thus, distances D_{26}-D_{29} are the same distances with the distance D_{26} being 1/4 of the distance between the first infusion site 1068 and the fifth infusion site 1076, the distance D_{27} being 1/2 of the distance between the first infusion site 1068 and the fifth infusion site 1076, the distance D_{28} being 3/4 of the distance between the first infusion site 1068 and the fifth infusion site 1076.

[0402] The distance D_{26} is located between the first infusion site 1068 and the second infusion site 1070. The distance D_{27} is located between the second infusion site 1070 and the third infusion site 1072. The distance D_{28} is located between the third infusion site 1072 and the fourth infusion site 1074. The distance D_{29} is located between the fourth infusion site

1074 and the fifth infusion site 1076. It is contemplated that the total infusion volumes and amount at each infusion sites may vary such as those embodiments described above.

[0403] Referring to FIG. 21, another embodiment of a prescriptive infusion approach is shown that uses a total infusion volume ($Vi_{(T)}$) of 1,500μL. FIG. 21 shows the cannula 1010 with six infusion sites 1100, 1102, 1104, 1106, 1108, 1110. The cannula 1010 infuses 100 μL (7% of the total infusion volume) of infusate at the first infusion site 1100. The cannula 1010 infuses 150 μL (10% of the total infusion volume) of infusate at the second infusion sites 1102. The cannula 1010 infuses 450 μL (300% of the total infusion volume) of infusate at the third infusion site 1104. The cannula 1010 infuses 400 μL (27% of the total infusion volume) of infusate at the fourth infusion site 1106. The cannula 1010 infuses 300 μL (20% of the total infusion volume) of infusate at the fifth infusion site 1108. The cannula 1010 infuses 100 μL (7% of the total infusion volume) of infusate at the sixth infusion site 1110. In this embodiment, the first segmental infusion volume, the second segmental infusion volume, the third segmental infusion volume, the fourth segmental infusion volume, the fifth segmental infusion volume and the sixth infusion volume are infused sequentially. It is contemplated that the total infusion volumes and amount at each infusion sites may vary such as described above.

[0404] The cannula 1010 initially moves to the first infusion site 1100 and infuses a first target segmental infusion volume of the infusate therein and distributes generally into a first segmental region 1112. The distal end 1010b of the cannula 1010 is advanced to a second infusion site 1102 and a second segmental infusion volume of the infusate is infused therein and distributes generally into the second target segmental region 1114. The distal end 1010b of the cannula 1010 is advanced to a third infusion site 1106 and a third segmental infusion volume of the infusate is infused therein and distributes generally into the third target segmental region 1116. The distal end 1010b of the cannula 1010 is advanced to a fourth infusion site 1106 and a fourth segmental infusion volume of the infusate is infused therein and distributes generally into the fourth target segmental region 1118. The distal end 1010b of the cannula 1010 is advanced to a fifth infusion site 1108 and a fifth segmental infusion volume of the infusate is infused therein and distributes generally into the fifth target segmental region 1120. The distal end 1010b of the cannula 1010 is advanced to a sixth infusion site 1110 and a sixth segmental infusion volume of the infusate is infused therein and distributes generally into the sixth target segmental region 1122.

[0405] The distance D_9 is shown in FIG. 21 between the posterior end 1020a and the anterior end 1020b of the putamen 1020 along its longitudinal axis. A distance D_{30} is shown between

the posterior end 1020a of the putamen 1020 and the first infusion site 1100. The distance D_{30} is generally from about 6 to about 12 mm in one embodiment. FIG. 21 also shows a distance D_{31} between the anterior end 1020b of the putamen 1020 and the sixth infusion site 1110. The distance D_{16} is generally from about 6 to about 8 mm.

[0406] The second infusion site 1102, the third infusion site 1104, the fourth infusion site 1106 and the fifth infusion site 1108 are located between the first infusion site 1100 and the sixth infusion site 1110. In one embodiment, each of the adjacent infusion sites (the first infusion site 1100, the second infusion site 1102, the third infusion site 1104, the fourth infusion site 1106, the fifth infusion site 1108, and the sixth infusion site 1110) are equally separated from each other as well. Thus, distances D_{32}-D_{36} are the same distances. The distance D_{32} is located between the first infusion site 1100 and the second infusion site 1102. The distance D_{33} is located between the second infusion site 1102 and the third infusion site 1104. The distance D_{34} is located between the third infusion site 1104 and the fourth infusion site 1106. The distance D_{35} is located between the fourth infusion site 1106 and the fifth infusion site 1108. The distance D_{36} is located between the fifth infusion site 1108 and the sixth infusion site 1110. It is contemplated that the distances between adjacent infusion sites may differ from each other.

[0407] The prescriptive infusion approaches can vary in the amount of time for completion. The prescriptive infusion approach generally is from about 4 to about 10 hours and, more specifically, is from about 5 to about 8 hours, or from about 5 to about 7 hours. The time is measured from the first cut to final suture.

[0408] The above described cannulae may be used in conjunction with a kit. The kit includes a plurality of components that assist in forming a low profile, anchoring device. These components assist in anchoring the cannula into a fixed position in, for example, a skull. These components in the kit are typically used to replace components such a ball joint array guide (BGJA), if used, when the cannula is used for longer durations of time. These components in the kit are often used, if applicable, after removal of the removable stylet when the cannula is used for longer durations of time. The components in the kits assist to reduce or inhibit damage to the tissue of the subject. In one embodiment, the plurality of kit components includes: (1) burr hole right-angle flexible cannula guide; (2) burr hole cover/fixation device; (3) cannula tunneling device (e.g., trocar); and (4) bone anchor.

[0409] Non-limiting examples of infusate including a therapeutic agent may be delivered through any of the cannulae discussed above include, but are not limited to, drugs, nanoparticles, biological agents (e.g., cells, virus, etc.).

[0410] In one embodiment, a vector may be used such as a nonviral vector or a viral vector. In one embodiment of any aspect, the vector is a DNA or RNA virus. Non-limiting examples of a viral vector include an AAV vector, an adenovirus vector, a lentivirus vector, a retrovirus vector, a herpesvirus vector, an alphavirus vector, a poxvirus vector, a baculovirus vector, and a chimeric virus vector. Non-limiting examples of AAV include AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, and any chimeras thereof. In some embodiments, AAV are AAV rhesus monkey serotype (AAV rh). Non limiting examples of AAV rh serotypes include AAV rh1, AAV rh2, AAV rh8, AAV rh10, AAV rh13, AAV rh20, AAV rh25, AAV rh32, AAV rh33, and AAV rh34AAV rh35, AAV rh36, AAV rh37, AAV rh38, AAV rh39, AAV rh40, AAV rh43, AAV rh48, AAV rh49, AAV rh50, AAV rh51, AAV rh52, AAV rh53, AAV rh54, AAV rh55, AAV rh57, AAV rh58, AAV rh61, AAV rh62, AAV rh64, and AAV rh74.

[0411] Any viral vector that is known in the art can be used with the cannula assembly and syringe combination. Examples of such viral vectors include, but are not limited to, vectors derived from: Adenoviridae; Birnaviridae; Bunyaviridae; Caliciviridae; Capillovirus group; Carlavirus group; Carmovirus virus group; Group Caulimovirus; Closterovirus Group; Commelina yellow mottle virus group; Comovirus virus group; Coronaviridae; PM2 phage group; Corcicoviridae; Group Cryptic virus; group Cryptovirus; Cucumovirus virus group Family ([PHgr]6 phage group); Cysioviridae; Group Carnation ringspot; Dianthovirus virus group; Group Broad bean wilt; Fabavirus virus group; Filoviridae; Flaviviridae; Furovirus group; Group Germinivirus; Group Giardiavirus; Hepadnaviridae; Herpesviridae; Hordeivirus virus group; Illarvirus virus group; Inoviridae; Iridoviridae; Leviviridae; Lipothrixviridae; Luteovirus group; Marafivirus virus group; Maize chlorotic dwarf virus group; icroviridae; Myoviridae; Necrovirus group; Nepovirus virus group; Nodaviridae; Orthomyxoviridae; Papovaviridae; Paramyxoviridae; Parsnip yellow fleck virus group; Partitiviridae; Parvoviridae; Peaenation mosaic virus group; Phycodnaviridae; Picornaviridae; Plasmaviridae; Prodoviridae; Polydnaviridae; Potexvirus group; Potyvirus; Poxviridae; Reoviridae; Retroviridae; Rhabdoviridae; Group Rhizidiovirus; Siphoviridae; Sobemovirus group; SSV 1-Type Phages; Tectiviridae; Tenuivirus; Tetraviridae; Group Tobamovirus; Group Tobravirus; Togaviridae; Group Tombusvirus; Group Torovirus; Totiviridae; Group Tymovirus; and Plant virus satellites.

[0412] An effective amount of a viral vector (e.g., a recombinant viral vector (rAAV)) is an amount sufficient to target an animal, or target a desired tissue. In some embodiments, an effective amount of a viral vector (e.g., a recombinant viral vector (rAAV)) is an amount

sufficient to produce a stable somatic transgenic animal model. The effective amount will depend primarily on factors such as the species, age, weight, health of the subject, and the tissue to be targeted, and may thus vary among animal and tissue.

[0413] In some embodiments, a dose of a therapeutic agent is administered to a subject no more than once per calendar day (e.g., a 24-hour period). In some embodiments, a dose of therapeutic agent is administered to a subject no more than once per 2, 3, 4, 5, 6, or 7 calendar days. In some embodiments, a dose of therapeutic agent is administered to a subject no more than once per calendar week (e.g., 7 calendar days). In some embodiments, a dose of therapeutic agent is administered to a subject no more than bi-weekly (e.g., once in a two calendar week period). In some embodiments, a dose of therapeutic agent is administered to a subject no more than once per calendar month (e.g., once in 30 calendar days). In some embodiments, a dose of therapeutic agent is administered to a subject no more than once per six calendar months. In some embodiments, a dose of therapeutic agent is administered to a subject no more than once per calendar year (e.g., 365 days or 366 days in a leap year).

[0414] Effective amounts, toxicity, and therapeutic efficacy can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the minimal effective dose and/or maximal tolerated dose. The dosage can vary depending upon the dosage form employed and the route of administration utilized. A therapeutically effective dose can be estimated initially from cell culture assays. Also, a dose can be formulated in animal models to achieve a dosage range between the minimal effective dose and the maximal tolerated dose. The effects of any particular dosage can be monitored by a suitable bioassay, e.g., assay for neuronal degradation or functionality among others. The dosage can be determined by a physician and adjusted, as necessary, to suit observed effects of the treatment.

[0415] In a further aspect of the above method, the viral vector is in a dosage of from about 1E8 to about 1.E13 vg/µl. The viral vector may be in a dosage of from about 0.7E9 to about 1.3E9 vg/µl. In another embodiment, the viral vector may be in a dosage of from about 0.7E9 to about 1.1E9 vg/µl. The viral vector may be delivered to a subject. The desired dosage should be in range between a minimally effective dose at the low end to a less than a mildly toxic level.

[0416] The dose calculation can be complicated, but is mandated by the tissue reaction to products delivered directly into the parenchyma of the striatum or another part of the brain. If the concentration is too weak (and the volume too small) there is no therapeutic effect. If more concentrated, the product may be effective. If the concentration is too high, it invokes

an inflammatory reaction and if sufficiently strong, it kills the cells at the infusion site.

[0417] After the dosage concentration is determined, the volume of that dilution is calculated that will be injected into each of the 4 striatal lobes. In humans and non-human primates (NHPs), the volumes are individually measured using MRI (2x putamina). The volume of product to be infused into each brain target to provide a likely percent coverage within the target structure is calculated based on the desired percent coverage of the measured target volume and the ratio of the volume of distribution (Vd)/infusion volume (Vi). For example, this percent coverage can range from 40% to 90%. A greater Vi may be required if higher percent coverage range may be required (e.g., 50% to 80%) in the target structures, based on imaging results and desired therapeutic effects. Typical healthy volumes for the putamen and caudate in human subjects are about 3.57 and about 2.73 cm^3, respectively, and about 0.55 and about 0.41 cm^3 in NHPs.

[0418] In one example, the volume delivered to NHPs would be in a volume range of from about 20 μL to about 250 μL. In a further example, the volume delivered to humans would be in a volume range of from about 140 μL to about 1.8 mL.

[0419] The dosages are delivered using the cannulae or cannula assemblies disclosed herein. Deliveries by a catheter or cannula, for example, into the extracellular fluid surround brain parenchyma requires overcoming the interstitial fluid pressure. Thus, in one method, very slow rates of infusion are gradually increased (2-3 infusion rates) to complete the delivery using bulk flow perfusion within the target extracellular space. This is generally referred to as "convection-enhanced delivery" or "CED." It is contemplated that other modified versions of the CED method of delivering fluid volumes within the brain, including methods using multiple (>3) increasing infusion rates, may be used.

[0420] Like all other contemplated therapeutic agents, viral vectors are delivered to a subject using the cannulae and a reservoir. For example, recombinant viral vector preferably suspended in a physiologically compatible carrier (i.e., in a composition), may be administered to a subject, i.e., host animal, such as a human, mouse, rat, cat, dog, sheep, rabbit, horse, cow, goat, pig, guinea pig, hamster, chicken, turkey, or a non-human primate (e.g., Macaque). In some embodiments, a host animal does not include a human.

[0421] Subjects to which the methods of the instant disclosure are applicable include veterinary subjects (e.g., dogs, cats, horses, etc.) and research animal subjects (e.g., mice, rats, rabbits, pigs, goats, sheep, primates, etc.), as well as human subjects. The methods are applicable to all primates, including simians. In some embodiments, the methods are applied to humans. In other embodiments, the methods are applied to non-human primates.

[0422] Any desired region or volume of a subject may be targeted according to the methods described herein. In some instances, the desired region or volume may be tissue including, but not limited to, a tissue of endodermal origin, a tissue of ectodermal origin, and a tissue mesodermal origin. Neural tissues are typically targeted. In some instances, neural tissues of the central nervous system (CNS) may be targeted including, for example, tissues of the brain and tissues of the spinal cord. In some instances, neural tissues of the peripheral nervous system may be targeted. It is contemplated that other tissue may be targeted according to the methods described herein.

[0423] In some instances, the methods may be applied for effective delivery/localization of an agent to a region of interest in the mammalian nervous system, including the central nervous system or the peripheral nervous system. Essentially any region of interest of the nervous system may be targeted according to the methods as described herein including, but not limited to, the brain, the spinal cord, the spinal ganglia, etc.

[0424] In some instances, the methods may be applied for effective delivery/localization of an agent to a region of interest in the mammalian brain. Essentially any region of interest of the brain may be targeted according to the methods as described herein.

[0425] Viral vectors described herein can be directly injected, into any region or area of the brain, such as, for example, occipital lobe, temporal lobe, parietal lobe, frontal lobe, cerebral cortex, cerebellum, hypothalamus, thalamus, pituitary gland, pineal gland, amygdala, hippocampus and the mid-brain.

[0426] In some instances, one or more brain lobes or a particular area within a brain lobe may be targeted including, but not limited to, the frontal lobe (either the entire frontal lobe or portions thereof including, but not limited to, Superior Frontal, Rostral Middle Frontal, Caudal Middle Frontal, Pars Opercularis, Pars Triangularis, and Pars Orbitalis, Lateral Orbitofrontal, Medial Orbitofrontal, Precentral, Paracentral, Frontal Pole, combinations thereof, and the like), parietal lobe (either the entire parietal lobe or portions thereof including, but not limited to, Superior Parietal, Inferior Parietal, Supramarginal, Postcentral, Precuneus, combinations thereof, and the like), temporal lobe (either the entire temporal lobe or portions thereof including, but not limited to, Superior Temporal, Middle Temporal, Inferior Temporal, Banks of the Superior Temporal Sulcus, Fusiform, Transverse Temporal, Entorhinal, Temporal Pole, Parahippocampal, combinations thereof, and the like) and occipital lobe (either the entire occipital lobe or portions thereof including, but not limited to, Lateral Occipital, Lingual, Cuneus, Pericalcarine, combinations thereof, and the like).

[0427] In some instances, one or more brain structures or a particular region or volume

within a brain structure may be targeted including, but not limited to, Hindbrain structures (e.g., Myelencephalon structures (e.g., Medulla oblongata, Medullary pyramids, Olivary body, Inferior olivary nucleus, Respiratory center, Cuneate nucleus, Gracile nucleus, Intercalated nucleus, Medullary cranial nerve nuclei, Inferior salivatory nucleus, Nucleus ambiguous, Dorsal nucleus of vagus nerve, Hypoglossal nucleus, Solitary nucleus, etc.), Metencephalon structures (e.g., Pons, Pontine cranial nerve nuclei, chief or pontine nucleus of the trigeminal nerve sensory nucleus (V), Motor nucleus for the trigeminal nerve (V), Abducens nucleus (VI), Facial nerve nucleus (VII), vestibulocochlear nuclei (vestibular nuclei and cochlear nuclei) (VIII), Superior salivatory nucleus, Pontine tegmentum, Respiratory centres, Pneumotaxic centre, Apneustic centre, Pontine micturition center (Barrington's nucleus), Locus coeruleus, Pedunculopontine nucleus, Laterodorsal tegmental nucleus, Tegmental pontine reticular nucleus, Raphe nuclei, Superior olivary complex, Paramedian pontine reticular formation, Cerebellar peduncles, Superior cerebellar peduncle, Middle cerebellar peduncle, Inferior cerebellar peduncle, Fourth ventricle, Cerebellum, Cerebellar vermis, Cerebellar hemispheres, Anterior lobe, Posterior lobe, Flocculonodular lobe, Cerebellar nuclei, Fastigial nucleus, Interposed nucleus, Globose nucleus, Emboliform nucleus, Dentate nucleus, etc.)), Midbrain structures (e.g., Tectum, Corpora quadrigemina, inferior colliculi, superior colliculi, Pretectum, Tegmentum, Periaqueductal gray, Parabrachial area, Medial parabrachial nucleus, Lateral parabrachial nucleus, Subparabrachial nucleus (Kolliker-Fuse nucleus), Rostral interstitial nucleus of medial longitudinal fasciculus, Midbrain reticular formation, Dorsal raphe nucleus, Red nucleus, Ventral tegmental area, Substantia nigra, Pars compacta, Pars reticulata, Interpeduncular nucleus, Cerebral peduncle, Crus cerebri, Mesencephalic cranial nerve nuclei, Oculomotor nucleus (Ill), Trochlear nucleus (IV), Mesencephalic duct (cerebral aqueduct, aqueduct of Sylvius), etc.), Forebrain structures (e.g., Diencephalon, Epithalamus structures (e.g., Pineal body, Habenular nuclei, Stria medullaris, Taenia thalami, etc.), Third ventricle, Thalamus structures (e.g., Anterior nuclear group, Anteroventral nucleus (aka ventral anterior nucleus), Anterodorsal nucleus, Anteromedial nucleus, Medial nuclear group, Medial dorsal nucleus, Midline nuclear group, Paratenial nucleus, Reuniens nucleus, Rhomboidal nucleus, Intralaminar nuclear group, Centromedial nucleus, Parafascicular nucleus, Paracentral nucleus, Central lateral nucleus, Central medial nucleus, Lateral nuclear group, Lateral dorsal nucleus, Lateral posterior nucleus, Pulvinar, Ventral nuclear group, Ventral anterior nucleus, Ventral lateral nucleus, Ventral posterior nucleus, Ventral posterior lateral nucleus, Ventral posterior medial nucleus, Metathalamus, Medial geniculate body, Lateral geniculate body, Thalamic reticular nucleus,

etc.), Hypothalamus structures (e.g., Anterior, Medial area, Parts of preoptic area, Medial preoptic nucleus, Suprachiasmatic nucleus, Paraventricular nucleus, Supraoptic nucleus (mainly), Anterior hypothalamic nucleus, Lateral area, Parts of preoptic area, Lateral preoptic nucleus, Anterior part of Lateral nucleus, Part of supraoptic nucleus, Other nuclei of preoptic area, median preoptic nucleus, periventricular preoptic nucleus, Tuberal, Medial area, Dorsomedial hypothalamic nucleus, Ventromedial nucleus, Arcuate nucleus, Lateral area, Tuberal part of Lateral nucleus, Lateral tuberal nuclei, Posterior, Medial area, Mammillary nuclei (part of mammillary bodies), Posterior nucleus, Lateral area, Posterior part of Lateral nucleus, Optic chiasm, Subfornical organ, Periventricular nucleus, Pituitary stalk, Tuber cinereum, Tuberal nucleus, Tuberomammillary nucleus, Tuberal region, Mammillary bodies, Mammillary nucleus, etc.), Subthalamus structures (e.g., Thalamic nucleus, Zona incerta, etc.), Pituitary gland structures (e.g., neurohypophysis, Pars intermedia (Intermediate Lobe), adenohypophysis, etc.), Telencephalon structures, white matter structures (e.g., Corona radiata, Internal capsule, External capsule, Extreme capsule, Arcuate fasciculus, Uncinate fasciculus, Perforant Path, etc.), Subcortical structures (e.g., Hippocampus (Medial Temporal Lobe), Dentate gyrus, Cornu ammonis (CA fields), Cornu ammonis area 1, Cornu ammonis area 2, Cornu ammonis area 3, Cornu ammonis area 4, Amygdala (limbic system) (limbic lobe), Central nucleus (autonomic nervous system), Medial nucleus (accessory olfactory system), Cortical and basomedial nuclei (main olfactory system), Lateral[disambiguation needed] and basolateral nuclei (frontotemporal cortical system), Claustrum, Basal ganglia, Striatum, Dorsal striatum (aka neostriatum), Putamen, Caudate nucleus, Ventral striatum, Nucleus accumbens, Olfactory tubercle, Globus pallidus (forms nucleus lentiformis with putamen), Subthalamic nucleus, Basal forebrain, Anterior perforated substance, Substantia innominata, Nucleus basalis, Diagonal band of Broca, Medial septal nuclei, etc.), Rhinencephalon structures (e.g., Olfactory bulb, Piriform cortex, Anterior olfactory nucleus, Olfactory tract, Anterior commissure, Uncus, etc.), Cerebral cortex structures (e.g., Frontal lobe, Cortex, Primary motor cortex (Precentral gyrus, Ml), Supplementary motor cortex, Premotor cortex, Prefrontal cortex, Gyri, Superior frontal gyrus, Middle frontal gyrus, Inferior frontal gyrus, Brodmann areas: 4, 6, 8, 9, 10, 11, 12, 24, 25, 32, 33, 44, 45, 46, 47, Parietal lobe, Cortex, Primary somatosensory cortex (S1), Secondary somatosensory cortex (S2), Posterior parietal cortex, Gyri, Postcentral gyrus (Primary somesthetic area), Other, Precuneus, Brodmann areas 1, 2, 3 (Primary somesthetic area); 5, 7, 23, 26, 29, 31, 39, 40, Occipital lobe, Cortex, Primary visual cortex (V1), V2, V3, V4, V5/MT, Gyri, Lateral occipital gyrus, Cuneus, Brodmann areas 17 (V1, primary visual cortex); 18, 19, Temporal

lobe, Cortex, Primary auditory cortex (Al), secondary auditory cortex (A2), Inferior temporal cortex, Posterior inferior temporal cortex, Superior temporal gyrus, Middle temporal gyrus, Inferior temporal gyrus, Entorhinal Cortex, Perirhinal Cortex, Parahippocampal gyrus, Fusiform gyrus, Brodmann areas: 9, 20, 21, 22, 27, 34, 35, 36, 37, 38, 41, 42, Medial superior temporal area (MST), Insular cortex, Cingulate cortex, Anterior cingulate, Posterior cingulate, Retrosplenial cortex, Indusium griseum, Subgenual area 25, and Brodmann areas 23, 24; 26, 29, 30 (retrosplenial areas); 31, 32, etc.)).

[0428] In some instances, one or more neural pathways or a particular portion of a neural pathway may be targeted including, but not limited to, neural pathways of those brain lobes and structures described above, Superior Longitudinal Fasciculus, Arcuate fasciculus, Cerebral peduncle, Corpus callosum, Pyramidal or corticospinal tract, Major dopamine pathways (dopamine system), Mesocortical pathway, Mesolimbic pathway, Nigrostriatal pathway, Striatonigral pathway, Tuberoinfundibular pathway, Serotonin Pathways serotonin system, Raphe Nuclei, Norepinephrine Pathways, and Locus coeruleus, etc.

[0429] Diseased neural tissues that may be targeted include, but are not limited to, neural tissue disease due to one or more of meningitis, encephalitis, multiple sclerosis (MS), stroke, brain tumors, epilepsy, Alzheimer's disease, AIDS-related dementia, Parkinson's disease, Multiple System Atrophy, Frontotemporal Dementia, and Huntington's disease.

[0430] Delivery of the compositions to a mammalian may be by, for example, any known means of delivering to a desired site, e.g., the central nervous system (CNS). It may be desirable to deliver the composition to the CNS of a subject. By "CNS" is meant all cells and tissue of the brain and spinal cord of a vertebrate. Thus, the term includes, but is not limited to, neuronal cells, glial cells, astrocytes, cerebrospinal fluid (CSF), intercellular interstitial spaces, and the like. Any composition described herein may be delivered directly to the CNS or brain by infusion into, for example, the ventricular region, as well as to the striatum (e.g., the caudate nucleus or putamen of the striatum), spinal cord and neuromuscular junction, or cerebellar lobule, with a needle, cannula, catheter or related device, using neurosurgical techniques known in the art, such as by stereotactic infusion. In some embodiments, compositions as described in the disclosure are administered by intravenous infusion. In some embodiments, compositions as described in the disclosure are administered by intraspinal infusion. In some embodiments, compositions as described in the disclosure are administered by intracerebro-ventricular infusion. In some embodiments, compositions are administered by intracerebral infusion. In some embodiments, compositions are administered by intrathecal infusion. In some embodiments, compositions are administered by intrastriatal

infusion. In some embodiments, compositions are delivered by intracranial infusion. In some embodiments, compositions are delivered by cisterna magna infusion. In some embodiments, compositions are delivered by cerebral lateral ventricle infusion.

[0431] The CNS includes, but is not limited to, certain regions of the CNS, neural pathways, somatosensory systems, visual systems, auditory systems, nerves, neuro endocrine systems, neuro vascular systems, brain neurotransmitter systems, and dural meningeal system.

[0432] Exemplary regions of the CNS include, but are not limited to, Myelencephalon; Medulla oblongata; Medullary pyramids; Olivary body; Inferior olivary nucleus; Rostral ventrolateral medulla; Caudal ventrolateral medulla; Solitary nucleus (Nucleus of the solitary tract); Respiratory center-Respiratory groups Dorsal respiratory group; Ventral respiratory group or Apneustic centre Pre-Bötzinger complex; Bötzinger complex; Retrotrapezoid nucleus; Nucleus retrofacialis; Nucleus retroambiguus; Nucleus para-ambiguus; Paramedian reticular nucleus; Gigantocellular reticular nucleus; Parafacial zone; Cuneate nucleus; Gracile nucleus; Perihypoglossal nuclei; Intercalated nucleus; Prepositus nucleus; Sublingual nucleus; Area postrema; Medullary cranial nerve nuclei; Inferior salivatory nucleus; Nucleus ambiguus; Dorsal nucleus of vagus nerve; Hypoglossal nucleus; Chemoreceptor trigger zone; Metencephalon; Pons; Pontine nuclei; Pontine cranial nerve nuclei; Chief or pontine nucleus of the trigeminal nerve sensory nucleus; Motor nucleus for the trigeminal nerve; Abducens nucleus (VI); Facial nerve nucleus (VII); Vestibulocochlear nuclei (vestibular nuclei and cochlear nuclei) (VIII); Superior salivatory nucleus; Pontine tegmentum; Pontine micturition center (Barrington's nucleus); Locus coeruleus; Pedunculopontine nucleus; Laterodorsal tegmental nucleus; Tegmental pontine reticular nucleus; Nucleus incertus; Parabrachial area; Medial parabrachial nucleus; Lateral parabrachial nucleus; Subparabrachial nucleus (Kölliker-Fuse nucleus); Pontine respiratory group; Superior olivary complex; Medial superior olive; Lateral superior olive; Medial nucleus of the trapezoid body; Paramedian pontine reticular formation; Parvocellular reticular nucleus; Caudal pontine reticular nucleus; Cerebellar peduncles; Superior cerebellar peduncle; Middle cerebellar peduncle; Inferior cerebellar peduncle; Fourth ventricle; Cerebellum Cerebellar vermis; Cerebellar hemispheres; Anterior lobe; Posterior lobe; Flocculonodular lobe; Cerebellar nuclei; Fastigial nucleus; Interposed nucleus; Globose nucleus; Emboliform nucleus; Dentate nucleus; Midbrain (mesencephalon); Tectum Corpora quadrigemina; Inferior colliculi; Superior colliculi; Pretectum; Tegmentum Periaqueductal gray; Rostral interstitial nucleus of medial longitudinal fasciculus; Midbrain reticular formation; Raphe Nuclear Complex, including the Dorsal raphe nucleus; Red nucleus; Ventral tegmental area; Parabrachial pigmented nucleus;

Paranigral nucleus; Rostromedial tegmental nucleus; Caudal linear nucleus; Rostral linear nucleus of the raphe; Interfascicular nucleus; Substantia nigra; Pars compacta; Pars reticulata; Interpeduncular nucleus; Cerebral peduncle; Crus cerebri; Mesencephalic cranial nerve nuclei; Oculomotor nucleus (III); Edinger-Westphal nucleus; Trochlear nucleus (IV); Mesencephalic duct (cerebral aqueduct, aqueduct of Sylvius); Forebrain (prosencephalon); Diencephalon; Epithalamus; Pineal body (pineal gland); Habenular nuclei; Stria medullaris; Taenia thalami; Third ventricle; Subcommissural organ; Thalamus; Anterior nuclear group; Anteroventral nucleus (a.k.a. ventral anterior nucleus); Anterodorsal nucleus; Anteromedial nucleus; Medial nuclear group; Medial dorsal nucleus; Midline nuclear group; Paratenial nucleus; Reuniens nucleus; Rhomboidal nucleus; Intralaminar nuclear group; Centromedian nucleus; Parafascicular nucleus; Paracentral nucleus; Central lateral nucleus; Lateral nuclear group; Lateral dorsal nucleus; Lateral posterior nucleus; Pulvinar; Ventral nuclear group Ventral anterior nucleus; Ventral lateral nucleus; Ventral posterior nucleus; Ventral posterior lateral nucleus; Ventral posterior medial nucleus; Metathalamus; Medial geniculate body; Lateral geniculate body; Thalamic reticular nucleus; Hypothalamus (limbic system) (HPA axis); Anterior Medial area Parts of preoptic area; Medial preoptic nucleus INAH 1; INAH 2; INAH 3; INAH 4; Median preoptic nucleus; Suprachiasmatic nucleus; Paraventricular nucleus; Supraoptic nucleus (mainly); Anterior hypothalamic nucleus; Lateral area; Parts of preoptic area; Lateral preoptic nucleus; Anterior part of Lateral nucleus; Part of supraoptic nucleus; Other nuclei of preoptic area; Median preoptic nucleus; Periventricular preoptic nucleus; Tuberal Medial area; Dorsomedial hypothalamic nucleus; Ventromedial nucleus; Arcuate nucleus; Lateral area Tuberal part of Lateral nucleus; Lateral tuberal nuclei; Posterior Medial area Mammillary nuclei (part of mammillary bodies); Posterior nucleus; Lateral area Posterior part of Lateral nucleus; Surface Median eminence; Mammillary bodies; Pituitary stalk (infundibulum); Optic chiasm; Subfornical organ; Periventricular nucleus; Tuber cinereum; Tuberal nucleus; Tuberomammillary nucleus; Tuberal region; Mammillary nucleus; Subthalamus (HPA axis); Subthalamic nucleus; Zona incerta; Pituitary gland (HPA axis); Neurohypophysis; Pars intermedia (Intermediate Lobe); Adenohypophysis; Telencephalon (cerebrum); Cerebral hemispheres; White matter; Centrum semiovale; Corona radiata; Internal capsule; External capsule; Extreme capsule; Subcortical; Hippocampus (Medial Temporal Lobe); Dentate gyrus; Cornu ammonis (CA fields); Cornu ammonis area 1 (CA1); Cornu ammonis area 2 (CA2); Cornu ammonis area 3 (CA3); Cornu ammonis area 4 (CA4); Amygdala (limbic system) (limbic lobe); Central nucleus (autonomic nervous system); Medial nucleus (accessory olfactory system); Cortical and basomedial nuclei (main

olfactory system); Lateral and basolateral nuclei (frontotemporal cortical system); Extended amygdala; Stria terminalis Bed nucleus of the stria terminalis; Claustrum; Basal ganglia; Striatum Dorsal striatum (a.k.a. neostriatum); Putamen; Caudate nucleus; Ventral striatum; Nucleus accumbens; Olfactory tubercle; Globus pallidus (forms nucleus lentiformis with putamen); Ventral pallidum; Subthalamic nucleus; Basal forebrain; Anterior perforated substance; Substantia innominata; Nucleus basalis; Diagonal band of Broca; Septal nuclei; Medial septal nuclei; Lamina terminalis; Vascular organ of lamina terminalis; Rhinencephalon (paleocortex); Olfactory bulb; Olfactory tract; Anterior olfactory nucleus; Piriform cortex; Anterior commissure; Uncus; Periamygdaloid cortex; Cerebral cortex (neocortex); Frontal lobe; Cortex Primary motor cortex (Precentral gyrus, M1); Supplementary motor cortex; Premotor cortex; Prefrontal cortex; Orbitofrontal cortex; Dorsolateral prefrontal cortex; Gyri Superior frontal gyrus; Middle frontal gyrus; Inferior frontal gyrus; Brodmann areas: 4, 6, 8, 9, 10, 11, 12, 24, 25, 32, 33, 44, 45, 46, 47; Parietal lobe Cortex Primary somatosensory cortex (S1); Secondary somatosensory cortex (S2); Posterior parietal cortex; Gyri Postcentral gyrus (Primary somesthetic area); Brodmann areas 1, 2, 3 (Primary somesthetic area); 5, 7, 23, 26, 29, 31, 39, 40; Occipital lobe Cortex Primary visual cortex (V1), V2, V3, V4, V5/MT; Gyri Lateral occipital gyrus; Brodmann areas 17 (V1, primary visual cortex); 18, 19; Temporal lobe Cortex Primary auditory cortex (A1); Secondary auditory cortex (A2); Inferior temporal cortex; Posterior inferior temporal cortex; Gyri Superior temporal gyrus; Middle temporal gyrus; Inferior temporal gyrus; Entorhinal cortex; Perirhinal cortex; Parahippocampal gyrus; Fusiform gyrus; Brodmann areas: 20, 21, 22, 27, 34, 35, 36, 37, 38, 41, 42; Insular cortex; Cingulate cortex Anterior cingulate; Posterior cingulate; Retrosplenial cortex; Indusium griseum; Subgenual area 25; and Brodmann areas 23, 24; 26, 29, 30 (retrosplenial areas); 31, and 32.

[0433] Exemplary neural pathways include, but are not limited to, Superior longitudinal fasciculus Arcuate fasciculus; Uncinate fasciculus; Perforant pathway; Thalamocortical radiations; Corpus callosum; Anterior commissure; Amygdalofugal pathway; Interthalamic adhesion; Posterior commissure; Habenular commissure; Fornix; Mammillotegmental; fasciculus; Incertohypothalamic pathway; Cerebral peduncle; Medial forebrain bundle; Medial longitudinal fasciculus; Myoclonic triangle; Solitary tract; Major dopaminergic pathways from dopaminergic cell groups; Mesocortical pathway; Mesolimbic pathway; Nigrostriatal pathway; Tuberoinfundibular pathway; Serotonergic pathways Raphe Nuclei; Norepinephrine Pathways Locus coeruleus and other noradrenergic cell groups; Epinephrine pathways from adrenergic cell groups; Glutamate and acetylcholine pathways from

mesopontine nuclei; Motor systems / Descending fibers; Extrapyramidal system; Pyramidal tract; Corticospinal tract; or Cerebrospinal fibers; Lateral corticospinal tract; Anterior corticospinal tract; Corticopontine fibers; Frontopontine fibers; Temporopontine fibers; Corticobulbar tract; Corticomesencephalic tract; Tectospinal tract; Interstitiospinal tract; Rubrospinal tract; Rubro-olivary tract; Olivocerebellar tract; Olivospinal tract; Vestibulospinal tract; Lateral vestibulospinal tract; Medial vestibulospinal tract; Reticulospinal tract; Lateral raphespinal tract; Alpha system; and Gamma system.

[0434] Exemplary somatosensory systems include, but are not limited to, Dorsal column–medial lemniscus pathway Gracile fasciculus; Cuneate fasciculus; Medial lemniscus; Spinothalamic tract; Lateral spinothalamic tract; Anterior spinothalamic tract; Spinomesencephalic tract; Spinocerebellar tract; Spino-olivary tract; and Spinoreticular tract.

[0435] Exemplary visual systems include, but are not limited to, Optic tract; Optic radiation; and Retinohypothalamic tract.

[0436] Exemplary auditory systems include, but are not limited to, Medullary striae of fourth ventricle; Trapezoid body; and Lateral lemniscus.

[0437] Exemplary nerves include, but are not limited to, Brain stem Cranial nerves Terminal (0); Olfactory (I); Optic (II); Oculomotor (III); Trochlear (IV); Trigeminal (V); Abducens (VI); Facial (VII); Vestibulocochlear (VIII); Glossopharyngeal (IX); Vagus(X); Accessory (XI); and Hypoglossal (XII).

[0438] Exemplary neuro-endocrine systems include, but are not limited to, Hypothalamic-pituitary hormones; HPA axis; HPG axis; HPT axis; and GHRH – GH.

[0439] Exemplary neuro-vascular systems include, but are not limited to, Middle cerebral artery; Posterior cerebral artery; Anterior cerebral artery; Vertebral artery; Basilar artery; Circle of Willis (arterial system); Blood-brain barrier; Glymphatic system; Venous systems; and Circumventricular organs.

[0440] Exemplary brain neurotransmitter systems include, but are not limited to, Noradrenaline system; Dopamine system; Serotonin system; Cholinergic system; GABA; Neuropeptides; Opioid peptides; Endorphins; Enkephalins; Dynorphins; Oxytocin; and Substance P.

[0441] Exemplary dural meningeal system include, but are not limited to, Brain-cerebrospinal fluid barrier; Meningeal coverings; Dura mater; Arachnoid mater; Pia mater; Epidural space; Subdural space; Subarachnoid space Arachnoid septum; Superior cistern; Cistern of lamina terminalis; Chiasmatic cistern; Interpeduncular cistern; Pontine cistern; Cisterna magna; Spinal subarachnoid space; Ventricular system; Cerebrospinal fluid; Third ventricle; Fourth

ventricle; Lateral ventricles Angular bundle; Anterior horn; Body of lateral ventricle; Inferior horn; Posterior horn Calcar avis; and Subventricular zone.

[0442] The "PNS" refers to the nerves and ganglia outside the brain and spinal cord. The main function of the PNS is to connect the CNS to the limbs and organs, essentially serving as a relay between the brain and spinal cord and the rest of the body. Unlike the CNS, the PNS is not protected by the vertebral column and skull, or by the blood-brain barrier, which leaves it exposed to, e.g., environmental and systemic toxins, and mechanical injuries.

[0443] The peripheral nervous system (PNS) is divided into the somatic nervous system and the autonomic nervous system. In the somatic nervous system, the cranial nerves are part of the PNS with the exception of the optic nerve (cranial nerve II), along with the retina. The second cranial nerve is not a true peripheral nerve but a tract of the diencephalon. Cranial nerve ganglia originated in the CNS. However, the remaining ten cranial nerve axons extend beyond the brain and are therefore considered part of the PNS. The autonomic nervous system exerts involuntary control over smooth muscle and glands. The connection between CNS and organs allows the system to be in two different functional states: sympathetic and parasympathetic.

[0444] As used herein, "neurological disease or disorder" can refer to any disease, disorder, or condition affecting or associated with the nervous system, i.e., those that affect the central nervous system (brain and spinal cord), the peripheral nervous system (peripheral nerves and cranial nerves), and the autonomic nervous system (parts of which are located in both central and peripheral nervous systems). More than 600 neurological diseases have been identified in humans. By way of non-limiting examples, the neurological disease or disorder includes Alzheimer's disease, Parkinson's disease, Huntington's disease, Canavan disease, Leigh's disease, spinal cerebral ataxia, Krabbe's disease, Batten's disease, Refsum disease, Tourette syndrome, primary lateral sclerosis, amyotrophic lateral sclerosis, progressive muscular atrophy, Pick's disease, muscular dystrophy, multiple sclerosis, myasthenia gravis, Binswanger's disease, trauma causing spinal cord or head injury, ophthalmic diseases and disorders, Tay-Sachs disease, Lesch-Nyan disease, epilepsy, cerebral infarcts, brain and spinal cord tumors, depression, bipolar affective disorder, persistent affective disorder, secondary mood disorder, schizophrenia, drug dependency, neuroses, psychosis, dementia, paranoia, attention deficit disorder, a psychosexual disorder, a sleeping disorder, a pain disorder, and/or a eating or weight disorder. In some embodiments, the neurological disease or disorder is a central nervous system (CNS) disease or disorder, e.g., Huntington's disease, Parkinson's disease, or Alzheimer's disease.

[0445] In one aspect, methods for treating neurological disorders involving the cortex, referred to herein as "cortical neurological disorders." The methods involve delivery of viral vectors described herein, or composition thereof to the CNS or PNS. Preferred cortical neurological disorders are those that involve large areas of the cortex, preferably more than one functional area of the cortex, preferably more than one lobe of the cortex, and up to and including the entire cortex. Preferred cortical neurological disorders include, but are not limited to, traumatic brain injury; stroke; enzymatic dysfunction disorders; psychiatric disorders, including post-traumatic stress syndrome; neurodegenerative diseases, including Huntington's disease, Parkinson's disease and Alzheimer's disease; epilepsy; neurooncologic disorders including primary (e.g., glioblastoma multiforme, astrocytoma, oligodendroglioma, ependymoma, meningioma) and secondary (metastatic) (e.g., breast, lung, renal, melanoma) tumors; and cognitive disorders, including dementias, autism, and depression. Preferred enzymatic dysfunction disorders include, but are not limited to, leukodystrophies, including Canavan's disease, and lysosomal storage diseases (LSD), including Niemann-Pick disease, Gaucher disease, Batten disease, Fabry disease and Pompe disease.

[0446] "Cortical neurological disorder", as used herein, refers to a neurological disorder involving the cortex. Cortical neurological disorders are neurological disorders that: (i) involve a population of cells in the cortex that is directly anatomically connected to the thalamus, and/or (ii) involve a population of cells that is directly anatomically connected to the cortical cell population in (i).

[0447] Preferred cortical neurological disorders are those that involve large areas of the cortex, preferably more than one functional area of the cortex, preferably more than one lobe of the cortex, and up to and including the entire cortex. Preferred cortical neurological disorders include, but are not limited to, traumatic brain injury; stroke; enzymatic dysfunction disorders; psychiatric disorders, including post-traumatic stress syndrome; neurodegenerative diseases, including Huntington's disease, Parkinson's disease and Alzheimer's disease; epilepsy; and cognitive disorders, including dementias, autism, and depression. Preferred enzymatic dysfunction disorders include, but are not limited to leukodystrophies, including Canavan's disease, and lysosomal storage diseases (LSD), including Niemann-Pick disease, Gaucher disease, Batten disease, Fabry disease and Pompe disease. This list of disorders is exemplary and non-limiting.

[0448] It will be apparent to the reasonably skilled artisan which neurological disorders are suitable for treatment by selected methods based on cortical pathology and neuroanatomical connectivity. "Cortex" as used herein refers to the cerebral cortex. In some embodiments, the

neurological disease or disorder is a CNS disease or disorder, e.g., Huntington's disease, Parkinson's disease, or Alzheimer's disease. In some embodiments, the neurological disease or disorder is a PNS disease or disorder, e.g., peripheral neuropathy.

[0449] According to one method, a viral vector is delivered to a central nervous system of a subject. The method includes providing one of the cannulae. The viral vector is provided and delivered to the central nervous system via the cannulae and the syringe combination.

[0450] The neurological disorder in this method includes, but is not limited to, meningitis, encephalitis, multiple sclerosis (MS), stroke, brain tumors, epilepsy, Alzheimer's disease, AIDS-related dementia, Parkinson's disease, Multiple System Atrophy, or Huntington's disease.

[0451] In the present invention, the viral vector comprises therapeutic nucleic acid (e.g., DNA or RNA) within its genome payload. The rAAV can comprise any nucleic acid having therapeutic benefit that fits the volumetric constraints of the vector. In some embodiments, the therapeutic nucleic acid is non-coding. For example, the therapeutic nucleic acid is non-coding RNA. Non-limiting examples of non-coding RNA are shRNA, siRNA, miRNA. In other embodiments, the therapeutic nucleic acid encodes therapeutic transgenes.

[0452] Non-limiting examples of therapeutic transgenes that can provide a therapeutic benefit for a disease or disorder of the CNS include CYP46A1 and HTT (For Huntington's), AADC and GDNF (for Parkinson's), GLB1 (for GM1), GDNF (for MSA), ASM (for Niemann-Pick), CYP46A1 (for Alzheimer's, ALS, MS and epilepsy), and UBE3A (for Angelman's). In some embodiments, the polypeptide-encoding transgene encodes an antibody or antigen-binding fragment thereof. Approaches for the treatment of CNS diseases or disorders can also: target metabolic pathways (e.g., CYP46A1 to clear protein-lipid rafts or protein aggregates for Huntington's, Parkinson's, ALS and Alzheimer's; similar approaches can also target synuclein and/or tau); use miRNA, shRNA and/or ribozyme meditated knockdown of undesirable mRNA transcripts (e.g., mHTT or HTT for Huntington's or ATS knockdown for Angelman's); use transgene expression for gene replacement (e.g., for restoring normal splicing by adding MBNL2 or SFRF6 in Huntington's, as well as more traditional gene replacement by expression of anti-synuclein antibodies, AADC, GDNF, or other transgenes). Diseases can include, among others, neurodegenerative diseases (Parkinson's, Huntington's, Alzheimer's, ALS, Multiple Sclerosis, epilepsy) and inborn mutations (AADC, Angelman, Newman-Pick, MPS, and others). Transgene-mediated gene editing is also contemplated, e.g., CRISPR or ARCUS or other gene editing technologies, including homologous recombination – this can be applied, for example, to Angelman

disease.

[0453] Example 1

[0454] A putaminal target volume is measured to be 4.1 cm^3, and has a mean Vd/Vi ratio of between about 2 to about 3 for putamina undergoing CED. Assuming, *arguendo,* that all the Vi is distributed within the target putamen, after delivering a Vi of 1500 µL, a volumetric measurement of MRI contrast agent volume within the putamen is performed. This may be performed using MRI images analyzed with volumetric software (e.g., Brainlab), and then find a Vd value for the visualized MRI contrast agent of 3.2 cm^3. The Vd/Vi ratio here, therefore, is equal to MRI contrast agent volume of 3.2 cm^3/1500 µL (or 3200 mm^3/1500 µL; or 3200 µL/1500 µL), which equates to a Vd/Vi ratio of 2.13. In addition, the putaminal percent coverage in this case equals 3.2 cm^3 (the volume of distribution (Vd) of the infusate as defined by the visualized MRI contrast agent) divided by 4.1 cm^3 (the putaminal target volume), times 100%, providing a percent coverage of the target putamen equal to 78% for this particular putaminal CED infusion.

[0455] Example 2

[0456] Calculations for Prescriptive Delivery to Putamen for Parkinson's Disease Using Trial Data

[0457] The baseline mean putaminal volumes were 3627 mm^3 or 3.627 cm^3 for the right putamen and 3741 mm^3 or 3.741 cm^3 for the left putamen. The anticipated putaminal volumes of distribution (Vd) needed for 65% coverage were calculated (1) right putamen – 0.65 x 3627 mm^3 = 2358 mm^3 and (2) left putamen – 0.65 x 3741 mm^3 = 2432 mm^3.

[0458] Assuming effective convection enhanced delivery (CED) for the first 1200 µL of Vi delivered bilaterally and using a Vd/Vi ratio for putamen of 2.3, 1200 µL of Vi should provide up to 2760 µL or mm^3 (2.3 x 1200 µL) of Vd. This indicates more than 300 µL (20%) of total Vi lost due to leakage/reflux, etc. and is much greater than the above calculated values of 2358 mm^3 and 2432 mm^3, respectively, for right and left putamina.

[0459] Considering the possibility that all the proposed Vi contributes to the Vd at the Vd/Vi ratio of 2.3, the projected Vd would then equal (1500 µL x 2.3) 3450 mm^3, or 3.45 cm^3, with an estimated putaminal coverage of the right putamen (3450/3627 x 100%) = 95% and the left putamen (3450/3741 x 100%) = 92%. Considering how low this Vd/Vi ratio can get using the above proposed infusion volumes before it is unlikely to meet the desired Vd requirements for 65% coverage, the minimum Vd/Vi ratio, for the right putamen was 2358

mm^3/1500 μL = 1.57 and the minimum Vd/Vi ratio of the left putamen was 2432 mm^3/1500 μL = 1.62.

[0460] Considering splitting the total infusion volume into what would be required within the projected 3 putaminal volumetric segments to attain adequate coverage, three segments (posterior, middle, and anterior segments) received 20%, 37%, and 43% of the total infusion volumes as discussed above in FIGS. 5-7. Using the above 1500 μL of Vi infusion, the Vi would be distributed into the following delivered volumes within the three putaminal volumetric segments: (1) posterior segments (first 10mm of putamen) receive 20%, or 300 μL of Vi; (2) middle segments (second 10mm of putamen) receive 37%, or 550 μL of Vi; and (3) anterior segments (third 10mm of putamen) receive 43%, or 650 μL of Vi.

[0461] Considering a 2.3 Vd/Vi for the putaminal segments, and assuming a 20% Vi loss due to extra-putaminal leakage (totaling up to a 300 μL loss of Vi out of the 1500 μL proposed), the following actual segmental Vi values were obtained: (1) posterior segments (first 10mm of putamen) received 300 minus 60 μL of Vi, or 240 μL of Vi; (2) middle segments (second 10mm of putamen) received 550 minus 110 μL of Vi, or 440 μL of Vi; and (3) anterior segments (third 10mm of putamen) received 650 minus 130 μL of Vi, or 520 μL of Vi. Continuing the calculation of Vd for each putaminal segment, using the 2.3 ratio, the following infusion volumes were obtained: (1) posterior segments (first 10mm of putamen), 240 μL of Vi yield 552 mm^3 of Vd; (2) middle segments (second 10mm of putamen), 440 μL of Vi yield 1012 mm^3 of Vd; and (3) anterior segments (third 10mm of putamen), 520 μL of Vi yield 1196 mm^3 of Vd.

[0462] All three segments in such a scenario, would total up to a Vd of 2760 mm^3, more than required for achieving a 65% coverage in calculation results for both right and left putaminal Vd. On the right putamen, 2760 mm^3 of Vd is 17% more than the calculated Vd of 2358 mm^3, and on the left putamen, 2760 mm^3 of Vd is 13.5% more than the calculated Vd of 2432 mm^3.

[0463] Example 3

[0464] Testing is performed in the operating room (OR) using a standard image-guided stereotactic platform and CT verification of a cannula positioning. Some non-limited examples of a standard image-guided stereotactic platform include Leksell Vantage™ stereotactic system or a Inomed stereotactic platform. Infusate distribution is not monitored or guided in real time via iMRI. In fact, iMRI is not used live or at all during the infusion of the infusate. The total volumetric putaminal coverage is expected to be determined about 60 minutes after the end of infusion following removal of part or all of the stereotactic guidance

frame. To assist in coverage-related decisions, immediate post-infusion coverage is estimated by time-dependent exponential regression methods.

[0465] Three subjects (6 putamina) are treated with AB-1005 using convection-enhanced delivery. The treatments are made in four different locations in each putamen. Specifically, a first location is 7-10mm from the posterior end of the putamina and the fourth location is 5-10mm from the anterior end of the putamina. Thus, it is expected to have 4 generally evenly spaced infusion stops within the putamen. In one example, the total volume of infusion ($Vi_{(T)}$) is 1,500µL, with 150µL being infused in the first location, 500µL in the second and third locations, and 350µL in the fourth location. The rate of infusion in each of the four locations is from about 3 to about 10µL/min. The rate of infusion is initially lower in the first location than the other three locations. The infusion is continued between the four locations.

[0466] The dose concentration is 3.3E12 vg/mL of the infusate. Each individual will be infused with 1.5mL per putamen (i.e., 3.0mL total). Thus, the total does of Ab-1005 delivered to each subject will be 9.9E12vg. The starting infusion rate is expected to be 3µL/min with a maximum infusion rate of 10µL/min.

[0467] After the total volume of infusion has been infused, the coverage of infusate in the putamen can be determined in each of the 3 individuals (6 total putamens). These variables can be varied so as to arrive at a therapeutic percent coverage of the putamen.

[0468] The infusate, as discussed above, will be distributed via diffusion from the infusion sites to locations throughout the putamen. In one non-limiting example using an average total infusion volume of 1,500 µL of infusate infused into 22 putamina, an average putaminal volume delivered was determined at various putaminal trajectory distances. Specifically, at 0mm putaminal trajectory distance, an average putaminal volume delivered was 62 µL; at 3mm, an average volume of 31µL was delivered; at 5mm, an average volume of 106µL was delivered; at 6mm, an average volume of 6µL was delivered; at 7mm, an average volume of 3µL was delivered; at 8mm, an average volume of 56µL was delivered; at 9mm, an average volume of 15µL was delivered; at 10mm, an average volume of 60µL was delivered; at 11mm, an average volume of 2µL was delivered; at 12mm, an average volume of 48µL was delivered; at 13mm, an average volume of 144µL was delivered; at 15mm, an average volume of 146µL was delivered; at 16mm, an average volume of 48µL was delivered; at 17mm, an average volume of 18µL was delivered; at 18mm, an average volume of 160µL was delivered; at 19mm, an average volume of 23µL was delivered; at 20mm, an average volume of 72µL was delivered; at 21mm, an average volume of 75µL was delivered; at 22mm, an average volume of 63µL was delivered; at 23mm, an average volume of 23µL was

delivered; at 24mm, an average volume of 53μL was delivered; at 25mm, an average volume of 21μL was delivered; at 26mm, an average volume of 152μL was delivered; at 27m, an average volume of 17μL was delivered; at 28m, an average volume of 48μL was delivered; at 29mm, an average volume of 17μL was delivered; at 33mm, an average volume of 31μL was delivered.

[0469] Throughout this disclosure, the numerical values represent approximate measures or limits to ranges to encompass minor deviations from the given values and embodiments having about the value mentioned as well as those having exactly the value mentioned. Other than in the working examples provided at the end of the detailed description, all numerical values of parameters (e.g., of quantities or conditions) in this specification, including the appended claims, are to be understood as being modified in all instances by the term "about" whether or not "about" actually appears before the numerical value. "About" indicates that the stated numerical value allows some slight imprecision (with some approach to exactness in the value; approximately or reasonably close to the value; nearly). If the imprecision provided by "about" is not otherwise understood in the art with this ordinary meaning, then "about" as used herein indicates at least variations that may arise from ordinary methods of measuring and using such parameters. For example, "about" may comprise a variation of less than or equal to 5%, optionally less than or equal to 4%, optionally less than or equal to 3%, optionally less than or equal to 2%, optionally less than or equal to 1%, optionally less than or equal to 0.5%, and in certain aspects, optionally less than or equal to 0.1%, or be within one standard deviation of a provided value.

[0470] In addition, described here are, unless specified otherwise, inclusive of endpoints and include disclosure of all distinct values and further divided ranges within the entire range. Thus, for example, a range of "from A to B" or "from about A to about B" is inclusive of A and of B. Disclosure of values and ranges of values for specific parameters (such as coverages, volumes, etc.) are not exclusive of other values and ranges of values useful herein. It is envisioned that two or more specific exemplified values for a given parameter may define endpoints for a range of values that may be claimed for the parameter. For example, if Parameter X is exemplified herein to have value A and also exemplified to have value Z, it is envisioned that Parameter X may have a range of values from about A to about Z. Similarly, it is envisioned that disclosure of two or more ranges of values for a parameter (whether such ranges are nested, overlapping or distinct) subsume all possible combination of ranges for the value that might be claimed using endpoints of the disclosed ranges. For example, if Parameter X is exemplified herein to have values in the range of 1-10, or 2-9, or 3-8, it is also

envisioned that Parameter X may have other ranges of values including 1-9, 1-8, 1-3, 1-2, 2-10, 2-8, 2-3, 3-10, and 3-9.

[0471] Although the disclosed embodiments have been illustrated and described with respect to one or more implementations, equivalent alterations and modifications will occur or be known to others skilled in the art upon the reading and understanding of this specification and the annexed drawings. In addition, while a particular feature of the invention may have been disclosed with respect to only one of several implementations, such feature may be combined with one or more other features of the other implementations as may be desired and advantageous for any given or particular application.

[0472] While various embodiments of the present invention have been described above, it should be understood that they have been presented by way of example only, and not limitation. Numerous changes to the disclosed embodiments can be made in accordance with the disclosure herein, without departing from the spirit or scope of the invention. Thus, the breadth and scope of the present invention should not be limited by any of the above described embodiments. Rather, the scope of the invention should be defined in accordance with the following claims and their equivalents.

CLAIMS

What is claimed is:

1. A method of implementing a total infusion volume ($Vi_{(t)}$) of an infusate into a target putamen of a subject in need thereof to achieve an infusate coverage of at least 40% in the target putamen, the method comprising:

providing a distance from a posterior end of the target putamen to an anterior end of the target putamen, the distance being along a longitudinal axis of the target putamen;

determining locations of a predetermined number of a plurality of infusion sites along the longitudinal axis based on the distance;

providing the total infusion volume ($Vi_{(t)}$) of the infusate to be infused into the target putamen, the total infusion volume being greater than 1000 μL;

determining a plurality of segmental infusion volumes, each segmental infusion volume of the plurality to be infused into a corresponding infusion site being selected from the plurality of infusion sites, a sum of the plurality of segmental infusion volumes being the total infusion volume ($Vi_{(t)}$);

inserting a cannula through a brain of the subject and positioning the cannula in the target putamen; and

infusing each of the plurality of segmental infusion volumes of the infusate into each of the corresponding plurality of infusion sites of the target putamen.

2. The method of claim 1, wherein determining the plurality of segmental infusion volumes is based on a database derived from sample segmental infusion volumes infused into sample infusion sites of sample putamens resulting in sample coverages.

3. The method of claim 1, further comprising verifying accurate placement of the cannula in the target putamen using intraoperative computed tomography (CT).

4. The method of claim 1, further comprising:

infusing a first segmental infusion volume ($Vi_{(1)}$) of the infusate into a first infusion site;

advancing a distal end of the cannula to a second infusion site and infusing a second segmental infusion volume ($Vi_{(2)}$) of the infusate into the second infusion site; and

repeating the advancing and infusion steps until each of the plurality of infusion sites has been infused with the infusate.

5. The method of claim 1, further comprising:

infusing a first segmental infusion volume ($Vi_{(1)}$) of the infusate into the first infusion site;

advancing a distal end of the cannula to a second infusion site and infusing a second segmental infusion volume ($Vi_{(2)}$) of the infusate into the second infusion site; and

advancing the distal end of the cannula to a third infusion site and infusing a third segmental infusion volume ($Vi_{(3)}$) of the infusate into the third infusion site.

6. The method of claim 5, further comprising:

advancing the distal end of the cannula to a fourth infusion site and infusing a fourth segmental infusion volume ($Vi_{(4)}$) of the infusate into the fourth infusion site.

7. The method of claim 1, wherein the infusate coverage by the infusate in the target putamen is from about 40% to about 90% of the volume of the target putamen of the subject.

8. The method of claim 7, wherein the infusate coverage by the infusate in the target putamen is from about 50% to about 80% of the volume of the target putamen of the subject.

9. The method of claim 1, wherein the infusing is performed with a syringe pump.

10. The method of claim 1, wherein the infusion occurs only at the plurality of infusion sites.

11. The method of claim 1, wherein the cannula comprises a stylet and further including removing the stylet without removing the cannula from the target putamen of the subject.

12. The method of claim 1, further including measuring the infusate coverage by the infusate in the target putamen after the total infusion volume ($Vi_{(T)}$) of the infusate has been infused.

13. The method of claim 12, wherein the measuring of the infusate coverage is performed using MRI.

14. The method of claim 1, wherein the total infusion volume ($Vi_{(T)}$) delivered to the target putamen is greater than 1200μL.

15. The method of claim 14, wherein the total infusion volume ($Vi_{(T)}$) delivered to the target putamen is greater than 1400μL.

16. The method of claim 1, wherein the total infusion volume ($Vi_{(T)}$) delivered to the target putamen is from about 1,000 to about 2,000μL.

17. The method of claim 16, wherein the total infusion volume ($Vi_{(T)}$) delivered to the target putamen is from about 1,300 to about 1,800μL.

18. The method of claim 1, wherein the infusate is infused to the plurality of infusion sites at a rate of from about 2 to about 12 μL/min.

19. The method of claim 18, wherein the rate is from about 3 to about 10 μL/min.

20. The method of claim 1, wherein the predetermined number of the plurality of infusion sites is 4, and where:

a first infusion site is from 3 mm to 8 mm from the posterior end of the target putamen;

a fourth infusion site is from 5 mm to 15 mm from the anterior end of the target putamen; and

a second infusion site and a third infusion site are 1/3 and 2/3 of a distance between the first and fourth infusion sites, respectively.

21. The method of claim 20, wherein the plurality of segmental infusion volumes is 4 infusion volumes, each of the 4 infusion volumes to be infused into one of the 4 infusion sites, and wherein:

a first segmental infusion volume is from 5% to 20% of the total infusion volume;

a second segmental infusion volume is from 25% to 35% of the total infusion volume;

a third segmental infusion volume is from 25% to 35% of the total infusion volume; and

a fourth segmental infusion volume is from 10% to 30% of the total infusion volume.

22. The method of claim 21, comprising:

infusing the first segmental infusion volume of the infusate into the first infusion site;

infusing the second segmental infusion volume of the infusate into the second infusion site;

infusing the third segmental infusion volume of the infusate into the third infusion site; and

infusing the fourth segmental infusion volume of the infusate into the fourth infusion site.

23. The method of claim 22, wherein the total infusion volume is about 1500 μL, the first segmental infusion volume is about 150 μL, the second segmental infusion volume is about 500 μL; the third segmental infusion volume is about 500 μL; and the fourth segmental infusion volume is about 350 μL.

24. The method of claim 23, wherein the cannula is positioned using preoperative imaging scans and without real-time MRI guidance.

25. A method of implementing a total infusion volume ($Vi_{(t)}$) of an infusate into a target putamen of a subject in need thereof to achieve a therapeutically effective coverage of the infusate in the target putamen, the method comprising:

providing a distance from a posterior end of the target putamen to an anterior end of the target putamen, the distance being along a longitudinal axis of the target putamen;

determining locations of at least three infusion sites along the longitudinal axis based on the distance,

a first of the at least three infusion sites being from 3 mm to 8 mm from the posterior end of the target putamen;

a last of the at least three infusion sites being from 5 mm to 15 mm from the anterior end of the target putamen; and

a remainder of the infusion sites being about equally spaced between the first and last infusion sites;

providing the total infusion volume ($Vi_{(t)}$) of the infusate to be infused into the target putamen, the total infusion volume being greater than 1000 μL;

determining at least three segmental infusion volumes to be independently infused into each of the at least three infusion sites, a sum of the segmental infusion volumes being the total infusion volume ($Vi_{(t)}$); and

infusing the at least three segmental infusion volumes of the infusate individually into the at least three infusion sites of the target putamen.

26. The method of claim 25, wherein the infusing comprises:

positioning a distal end of a cannula at the first one of the at least three infusion sites and infusing a first of the at least three segmental infusion volume of the infusate into the first of the at least three infusion sites;

advancing the distal end of the cannula to a second of the least three infusion sites and infusing a second of the at least three segmental infusion volumes of the infusate into the second of the at least three infusion sites; and

repeating the advancing and the infusing until a last of the at least three segmental infusion volumes of the infusate has been infused into the last of the at least three infusion sites.

27. The method of claim 25, wherein determining the at least three segmental infusion volumes is based on a database derived from sample segmental infusion volumes infused into sample infusion sites of sample putamens resulting in sample coverages.

28. The method of claim 25, wherein the determining locations of at least three infusion sites comprises determining locations of only a first infusion site, a second infusion site, and a third infusion site, the first infusion site being the first of the least three infusion sites, the third infusion site being the last of the at least three infusion sites, and the second infusion site being about midway between the first and the third infusion sites.

29. The method of claim 28, wherein the determining the least three segmental infusion volumes comprises determining a first segmental infusion volume to be infused into the first infusion site, a second segmental infusion volume to be infused into the second infusion site, and a third segmental infusion volume to be infused into the third infusion site, and wherein:

the first segmental infusion volume is 5-40% of the total infusion volume;

the second segmental infusion volume is 33-80% of the total infusion volume; and

the third segmental infusion volume is 7-47% of the total infusion volume.

30. The method of claim 25, wherein the determining locations of at least three infusion sites comprises determining locations of only a first infusion site, a second infusion site, a third infusion site, and a fourth infusion site, the first infusion site being the first of the least three infusion sites, the fourth infusion site being the last of the at least three infusion sites, and the second and third infusion sites being about 1/3 and about 2/3 of the distance between the first and fourth infusion sites, respectively.

31. The method of claim 30, wherein the determining the least three segmental infusion volumes comprises determining a first segmental infusion volume to be infused into the first infusion site, a second segmental infusion volume to be infused into the second infusion site, a third segmental infusion volume to be infused into the third infusion site, and a fourth segmental infusion volume to be infused into the fourth infusion site, and wherein:

the first segmental infusion volume is from 2% to 27% of the total infusion volume;

the second segmental infusion volume is from 20% to 47% of the total infusion volume;

the third segmental infusion volume is from 20% to 47% of the total infusion volume; and

the fourth segmental infusion volume is from 7% to 40% of the total infusion volume.

32. The method of claim 25, wherein the determining locations of at least three infusion sites comprises determining locations of only a first infusion site, a second infusion site, a third infusion site, a fourth infusion site, and a fifth infusion site, the first infusion site being the first of the least three infusion sites, the fifth infusion site being the last of the at least three infusion sites, and the second, third, and fourth infusion sites being about ¼, about ½, and about ¾ of the distance between the first and fifth infusion sites, respectively.

33. The method of claim 32, wherein the determining the least three segmental infusion volumes comprises determining a first segmental infusion volume to be infused into the first infusion site, a second segmental infusion volume to be infused into the second infusion site, a third segmental infusion volume to be infused into the third infusion site, a fourth segmental infusion volume to be infused into the fourth infusion site, and a fifth segmental infusion volume to be infused into the fifth infusion site, and wherein:

the first segmental infusion volume is 2-27% of the total infusion volume;

the second segmental infusion volume is 3-23% of the total infusion volume;

the third segmental infusion volume is 20-47% of the total infusion volume;

the fourth segmental infusion volume is 10-37% of the total infusion volume; and

the fifth segmental infusion volume is 3-27% of the total infusion volume.

34. The method of claim 25, wherein the therapeutically effective coverage is greater than 40%.

35. A method of implementing a total infusion volume ($Vi_{(t)}$) of an infusate into a target putamen of a subject in need thereof to achieve an infusate coverage of at least 40% in the target putamen, the method comprising:

verifying the accuracy of the placement of the cannula in the absence of magnetic resonance imaging (MRI);

infusing a first segmental infusion volume of the infusate into a first infusion site using a cannula;

advancing a distal end of the cannula to a second infusion site and infusing a second segmental infusion volume of the infusate into the second infusion site;

advancing the distal end of the cannula to a third infusion site and infusing a third segmental infusion volume of the infusate into the third infusion site; and

advancing the distal end of the cannula to a fourth infusion site and infusing a fourth segmental infusion volume of the infusate into the fourth infusion site,

wherein the second and third infusion sites are located between the first and fourth infusion sites.

wherein the aggregate of the first segmental infusion volume, the second segmental infusion volume, the third segmental infusion volume, and the fourth segmental infusion volume is a total infusion volume delivered to the target putamen, the total infusion volume ($Vi_{(T)}$) being greater than 1,000μL, the first segmental infusion volume being from about 2 to about 27% of the total infusion volume, the second segmental infusion volume being from about 20 to about 47% of the total infusion volume, the third segmental infusion volume being from about 20 to about 47% of the total infusion volume, the fourth segmental infusion volume being from about 7 to about 40% of the total infusion volume.

36. The method of claim 35, wherein the infusate coverage by the infusate in the target putamen is from about 40% to about 90% of a volume of the target putamen of the subject.

37. The method of claim 36, wherein the infusate coverage by the infusate in the target putamen is from about 50% to about 80% of the volume of the target putamen of the subject.

38. The method of claim 35, wherein the total infusion volume delivered to the target putamen is from about 1,000µL to about 2,000µL.

39. The method of claim 38, wherein the total infusion volume delivered to the target putamen is from about 1,200µL to about 1,800µL.

40. The method of claim 39, wherein the total infusion volume delivered to the target putamen is from about 1,400µL to about 1,600µL.

41. The method of claim 35, wherein the first segmental infusion volume is from about 5 to about 25% of the total infusion volume ($Vi_{(T)}$), the second segmental infusion volume being from about 20 to about 40% of the total infusion volume, the third segmental infusion volume being from about 20 to about 40% of the total infusion volume, and the fourth segmental infusion volume being from about 10 to about 35% of the total infusion volume such that the percent coverage by the infusate in the target putamen is at least 50% of the volume of the target putamen of the subject.

42. The method of claim 41, wherein the first segmental infusion volume is from about 5 to about 25% of the total infusion volume ($Vi_{(T)}$), the second segmental infusion volume being from about 25 to about 35% of the total infusion volume, the third segmental infusion volume being from about 25 to about 35% of the total infusion volume, and the fourth segmental infusion volume being from about 10 to about 30% of the total infusion volume such that the percent coverage by the infusate in the putamen is at least 50% of the volume of the target putamen of the subject.

43. The method of claim 35, wherein the first infusion site is located near a posterior end of the target putamen and the fourth infusion site is located near an anterior end of the target putamen, the second infusion site being located approximately equidistance between the first infusion site and the third infusion site, the third infusion site being located approximately equidistance between the second infusion site and the fourth infusion site.

44. The method of claim 35, wherein the first infusion site is from about 3 to about 8mm from the posterior end of the target putamen, and the fourth infusion site is from about 5 to about 15mm from the anterior end of the target putamen.

45. The method of claim 35, wherein the first segmental infusion volume, the second segmental infusion volume, the third segmental infusion volume, and the fourth segmental infusion volume are infused sequentially.

46. The method of claim 35, wherein the cannula comprises a stylet and further including removing the stylet without removing the cannula from the target putamen of the subject.

47. The method of claim 35, further including measuring the infusate coverage by the infusate in the target putamen after the total infusion volume ($Vi_{(t)}$) of the infusate has been infused.

48. The method of claim 35, wherein a rate of the infusate to the target infusion sites of the target putamen is from about 2 to about 12 μL/min.

49. A system to determine segmental infusion volumes ($Vi_{1(t)} + Vi_{2(t)} \ldots + Vi_{n(t)}$) of an infusate to individually administer to each of a plurality of target segmental regions of a target putamen of a subject to achieve a desired percent coverage of the infusate within the target putamen, the system comprising:

an input interface to receive data on a target putaminal volume ($Vp_{(t)}$) of the target putamen, a number of the plurality of target segmental regions of the target putamen, and the desired percent coverage;

a storage device storing:

(1) sample putaminal volumes ($Vp_{(s)}$) obtained from sample putamina from a set of sample subjects wherein each sample putamen has a plurality of sample segmental regions;

(2) sample infusion volumes ($Vi_{(s)}$) of the infusate infused to each sample segmental region of each sample putamen, wherein a sum of the sample infusion volumes infused into each of the sample segmental regions of each sample putamen is a total sample infusion volume ($Vi_{1(s)} + Vi_{2(s)} \ldots + Vi_{n(s)} = Vi_{T(s)}$);

(3) sample volumes of distribution ($Vd_{(s)}$) of the infusate for each sample putamen, each sample volume of distribution ($Vd_{(s)}$) being a volume of the total sample infusion volume ($Vi_{T(s)}$) retained within each sample putamen; and

(4) a sample percent coverage for the infusate in each sample putamen, each sample percent coverage calculated by dividing each sample volume of distribution ($Vd_{(s)}$) by the corresponding sample putaminal volume ($Vp_{(s)}$);

a processor coupled to the input interface and the storage device, the processor configured to determine the total infusion volume ($Vi_{1(t)} + Vi_{2(t)} \ldots + Vi_{n(t)} = Vi_{(T)}$) of the infusate to infuse into the target putamen and the infusion volumes ($Vi_{1(t)} + Vi_{2(t)} \ldots + Vi_{n(t)}$) to infuse into each target segmental region of the target putamen based on:

(a) the desired percent coverage;

(b) the number of the plurality of target segmental regions of the target putamen;

(c) the target putaminal volume ($Vp_{(t)}$); and

(d) a plurality of stored sample data selected from the following: the sample putaminal volumes ($Vp_{(s)}$), a number of sample segmental regions per sample putamen, the sample infusion volumes, the total sample infusion volumes, the sample volumes of distribution, the sample percent coverages, and combinations thereof; and

an output interface coupled to the processor, the output interface providing the total infusion volume ($Vi_{(T)}$) of the infusate to administer to the target putamen and the segmental infusion volumes to individually administer to each of the plurality of target segmental regions of the target putamen to achieve the desired percent coverage of the infusate.

50. The system of claim 49, wherein the processor is further configured to determine sample volumes of distribution; determine the total sample infusion volume ratio ($Vd_{(s)}/Vi_{T(s)}$ ratio); and determine the total infusion volume ($Vi_{(T)}$) of the infusate to administer to the target putamen to achieve the desired percent coverage using the $Vd_{(s)}/Vi_{T(s)}$ ratio.

51. The system of claim 50, wherein the $Vd_{(s)}/Vi_{T(s)}$ ratio is from about 1.5 to about 2.5.

52. The system of claim 51, wherein the $Vd_{(s)}/Vi_{T(s)}$ ratio is from about 2 to about 2.25.

53. The system of claim 49, wherein the target putaminal volume of the subject is determined by magnetic resonance imaging (MRI).

54. The system of claim 49, wherein the desired percent coverage by the infusate in the target putamen is from about 40% to about 90% of the target putaminal volume ($Vp_{(T)}$).

55. The system of claim 54, wherein the desired percent coverage by the infusate in the target putamen is from about 50% to about 80% of the target putaminal volume ($Vp_{(T)}$).

56. A method of determining segmental infusion volumes of an infusate to infuse into each of a plurality of target segmental regions of a target putamen of a subject in need thereof to achieve a desired percent coverage of the infusate within the target putamen using a system including an input interface, a storage device, a processor and an output interface, the processor coupled to the input interface and the storage device, the output interface coupled to the processor, the method comprising:

entering a target putaminal volume ($Vp_{(t)}$) of the target putamen, a number of target segmental regions of the target putamen, and the desired percent coverage into the input interface of the system; and

receiving from the output interface of the system, the total infusion volume ($Vi_{(t)}$) of the infusate to administer to the target putamen and the segmental infusion volumes to individually administer to each of the plurality of target segmental regions of the target putamen to achieve the desired percent coverage of the infusate.

57. The method of claim 56, further comprising infusing the segmental infusion volumes of the infusate to each of the plurality of target segmental regions of the target putamen.

58. The method of claim 57, wherein the infusing is performed without magnetic resonance imaging (MRI).

59. The method of claim 57, further comprising:

inserting a cannula through a brain of the subject to the target putamen;

infusing a first segmental infusion volume of the infusate into the first segmental region;

advancing the distal end of the cannula to a second segmental region and infusing a second segmental infusion volume of the infusate into the second segmental region; and

repeating the advancing and infusing steps until each of the plurality of target segmental regions has been infused with the infusate.

60. The method of claim 57, wherein the infusing is performed with a syringe pump.

61. The method of claim 57, wherein the infusing is performed with a cannula that is capable of infusing the infusate to the plurality of target segmental regions simultaneously.

62. The method of claim 61, wherein the infusing is performed with a syringe pump.

63. The method of any one of claims 59-62, wherein the cannula comprises a stylet that is removeable from the cannula without removing the cannula from the target putamen.

64. The method of any one of claims 59-62, wherein the cannula is inserted into the brain using magnetic resonance imaging (MRI) guidance, and wherein the MRI is not utilized during the infusing.

65. The method of claim 56, wherein the total infusion volume ($Vi_{(T)}$) of the infusate is delivered to a posterior segmental region of the target putamen, a middle segmental region of the target putamen, and an anterior segmental region of the target putamen.

66. The method of claim 56, wherein the total infusion volume ($Vi_{(T)}$) of the infusate includes a first infusion volume ($Vi_{1(t)}$), a second infusion volume ($Vi_{2(t)}$), and a third infusion volume ($Vi_{3(t)}$).

67. The method of claim 66, wherein the first infusion volume ($Vi_{1(t)}$) is from about 10% to about 30% of the total infusion volume ($Vi_{(T)}$), the second infusion volume ($Vi_{2(t)}$) is from about 30% to about 50% of the total infusion volume ($Vi_{(T)}$), and the third infusion volume ($Vi_{3(t)}$) is from about 30% to about 50% of the total infusion volume ($Vi_{(T)}$).

68. The method of claim 67, wherein the first infusion volume ($Vi_{1(t)}$) is from about 15% to about 25% of the total infusion volume ($Vi_{(T)}$), the second infusion volume ($Vi_{2(t)}$) is from about 35% to about 40% of the total infusion volume ($Vi_{(T)}$), and the third infusion volume ($Vi_{3(t)}$) is from about 40% to about 45% of the total infusion volume ($Vi_{(T)}$).

69. The method of claim 68, wherein the first infusion volume ($Vi_{1(t)}$) is calculated to be delivered to a posterior segmental region of the target putamen, the second infusion volume ($Vi_{2(t)}$) is calculated to be delivered to a middle segmental region of the target putamen, and the third infusion volume ($Vi_{3(t)}$) is calculated to be delivered to an anterior segmental region of the target putamen.

70. The method of claim 56, wherein the desired percent coverage by the infusate in the target putamen is from about 40% to about 90% of the target putaminal volume ($Vp_{(T)}$).

71. The method of claim 70, wherein the desired percent coverage by the infusate in the target putamen is from about 50% to about 80% of the target putaminal volume ($Vp_{(T)}$).

72. A system to determine a total infusion volume ($Vi_{(T)}$) of an infusate to administer to a target putamen of a subject to achieve a desired percent coverage of the infusate within the target putamen, the system including:

an input interface to receive data on a target putaminal volume ($Vp_{(t)}$) of the target putamen and the desired percent coverage;

a storage device storing: (1) sample putaminal volumes ($Vp_{(s)}$) obtained from sample putamina from a set of sample subjects; (2) a total sample infusion volume ($Vi_{T(s)}$) of the infusate to each sample putamen; (3) sample volumes of distribution ($Vd_{(s)}$) being a volume of the total sample infusion volume ($Vi_{T(s)}$) retained within each sample putamen; and (4) a sample percent coverage for the infusate in each sample putamen by dividing each sample volume of distribution ($Vd_{(s)}$) by the corresponding sample putaminal volume ($Vp_{(s)}$);

a processor coupled to the input interface and the storage device, the processor configured to determine the total infusion volume ($Vi_{(T)}$) of the infusate to infuse into the target putamen based on the target putaminal volume ($Vp_{(t)}$) of the subject, the desired percent coverage and a plurality of stored sample data selected from the following: the sample putaminal volumes ($Vp_{(s)}$), the total sample infusion volumes ($Vi_{T(s)}$), the sample volumes of distribution ($Vd_{(s)}$), the sample percent coverages, and combinations thereof; and

an output interface coupled to the processor, the output interface providing the total infusion volume ($Vi_{(T)}$) of the infusate to administer to the target putamen to achieve the desired percent coverage of the infusate.

73. The system of claim 72 further comprising an infusion control system configured to regulate infusion of the infusate to the target putamen, the infusion control system including at least one pump to infuse the infusate at a determined rate of infusion for the total infusion volume ($Vi_{(T)}$).

74. The system of claim 73, wherein the infusion control system includes a cannula to allow simultaneous infusion of the infusate into two or more target segmental regions of the target putamen.

75. The system of claim 72 further comprising a display coupled to the output interface, the display operable to display the total infusion volume ($Vi_{(T)}$) of the infusate.

76. The system of claim 72, wherein the desired percent coverage by the infusate in the target putamen is from about 40% to about 90% of the target putaminal volume ($Vp_{(T)}$).

77. The system of claim 76, wherein the desired percent coverage by the infusate in the target putamen is from about 50% to about 80% of the target putaminal volume ($Vp_{(T)}$).

78. A method to provide a training set to a machine learning model to predict a total infusion volume ($Vi_{(T)}$) of an infusate to administer to each of a plurality of target segmental regions of a target putamen of a subject to achieve a desired percent coverage of the infusate within the target putamen, the method comprising:

obtaining sample putaminal volumes ($Vp_{(s)}$) from a set of sample subjects by scanning each putamen of each of the set of sample subjects via a scanner, wherein each sample putamen has a plurality of sample segmental regions;

infusing at least one sample infusion volume ($Vi_{(s)}$) of the infusate to each sample segmental region of each sample putamen via a cannula, wherein a volume of each of the at least one sample infusion volume ($Vi_{(s)}$) retained within each sample segmental region is a sample volume of distribution ($Vd_{(s)}$) of the infusate, wherein a sum of the at least one sample infusion volume for each of the plurality of sample segmental regions infused into each sample putamen is a total sample infusion volume ($Vi_{1(s)} + Vi_{2(s)} \ldots + Vi_{n(s)} = Vi_{T(s)}$) and a volume of the total sample infusion volume ($Vi_{T(s)}$) retained within each sample putamen is the sample volume of distribution ($Vd_{(s)}$);

determining a sample percent coverage for the infusate in each sample putamen by dividing each sample volume of distribution ($Vd_{(s)}$) by the corresponding sample putaminal volume ($Vp_{(s)}$);

determining the total infusion volume ($Vi_{(T)}$) of the infusate to administer to the plurality of target segmental regions of the target putamen to achieve the desired percent coverage of the infusate based on a target putaminal volume ($Vp_{(T)}$) and a plurality of sample data selected from the following: the sample putaminal volumes ($Vp_{(s)}$), a number of sample segmental regions per sample putamen, the sample infusion volumes ($Vi_{(s)}$), the total sample infusion volumes ($Vi_{(T)}$), the sample volumes of distribution ($Vd_{(s)}$), the sample percent coverages, and combinations thereof;

preparing the training set having inputs of the determined sample putaminal volumes, the determined total sample infusion volumes, the determined total sample volumes of distribution, and the determined sample percent coverages; and

training a machine learning model via the training set to predict the total infusion volume of the infusate based on inputs of the target putaminal volume and the desired sample percent coverage of the infusate.

79. The method of claim 78, wherein the infusate comprises a contrast agent and the sample volumes of distribution ($Vd_{(s)}$) is determined by visualizing the contrast agent in the infusate by magnetic resonance imaging (MRI).

80. The method of claim 78, wherein the sample volumes of distribution ($Vd_{(s)}$) is determined after all of the at least one sample infusion volumes have been infused into each of the sample putamina.

81. A computer-implemented method to predict a plurality of infusion volumes ($Vi_{(T)}$) of an infusate to administer to each of a plurality of target segmental regions of a target putamen of a subject to achieve a desired percent coverage of the infusate within the target putamen, the method comprising:

determining sample putaminal volumes ($Vp_{(s)}$) from a set of sample subjects, each sample putamen having a plurality of sample segmental regions;

determining a sample percent coverage for the infusate in each sample putamen by dividing each total sample volume of distribution ($Vd_{(s)}$) by the corresponding sample putaminal volume ($Vp_{(s)}$) via a processor, wherein each sample volume of distribution is

obtained from infusing a sample infusion volume ($Vi_{(s)}$) of the infusate to each sample segmental region of each sample putamen via a cannula, wherein a volume of each sample infusion volume ($Vi_{(s)}$) retained within each sample segmental region is a sample volume of distribution ($Vd_{(s)}$), wherein a sum of the at least one sample infusion volume for each of the plurality of segmental regions infused into each sample putamen is a total sample infusion volume ($Vi_{1(s)} + Vi_{2(s)} \ldots + Vi_{n(s)} = Vi_{T(s)}$) and a volume of the total sample infusion volume ($Vi_{T(s)}$) retained within each sample putamen is the sample volume of distribution ($Vd_{(s)}$);; and

via the processor, determining the total infusion volume ($Vi_{(T)}$) of the infusate to administer to the plurality of target segmental regions of the target putamen to achieve the desired coverage of the infusate based on a target putaminal volume ($Vp_{(t)}$) and a plurality of sample factors selected from the following: the sample putaminal volumes ($Vp_{(s)}$), a number of sample segmental regions per sample putamen, the sample infusion volumes ($Vi_{(s)}$), the total sample infusion volumes ($Vi_{(T)}$), the sample volumes of distribution ($Vd_{(s)}$), the sample percent coverages, and combinations thereof.

82. The computer-implemented method of claim 81, further comprising determining an infusion time and an infusion rate for infusing the total infusion volume ($Vi_{(T)}$) of the infusate via the processor.

83. The computer-implemented method of claim 81, wherein the infusate includes a therapeutic agent being selected from the group consisting of a viral therapeutic, a DNA therapeutic, an RNA therapeutic, a protein therapeutic, therapeutic nanoparticles, and a small molecule compound.

84. The computer-implemented method of claim 81, wherein the sample infusion volume ($Vi_{(s)}$) is delivered to at least two of the plurality of segmental regions of each sample putamen via the cannula.

85. The computer-implemented method of claim 84, wherein the sample infusion volume ($Vi_{(s)}$) is delivered to at least three of the plurality of segmental regions of each sample putamen via the cannula.

86. The computer-implemented method of claim 81, wherein the plurality of segmental regions of each sample putamen is selected from the group consisting of a posterior segmental region of the putamen, a middle segmental region of the putamen, an anterior segmental region of the putamen, and combinations thereof.

87. The computer-implemented method of claim 81, wherein a first sample infusion volume ($Vi_{1(s)}$) is delivered to a first segmental region of each sample putamen via the cannula and a second sample infusion volume ($Vi_{2(s)}$) is delivered to each second segmental region of the sample putamen via the cannula, the first and second sample infusion volumes of each sample putamen provide a respective total sample infusion volume.

88. The computer-implemented method of claim 81, wherein a first sample infusion volume ($Vi_{1(s)}$) is delivered to a first segmental region of each sample putamen via the cannula, a second sample infusion volume ($Vi_{2(s)}$) is delivered to a second segmental region of each sample putamen via the cannula, and a third sample infusion volume ($Vi_{3(s)}$) is delivered to a third segmental region of each sample putamen via the cannula, the first, second and third sample infusion volumes of each sample putamen provide a respective total sample infusion volume ($Vi_{T(s)}$).

89. The computer-implemented method of claim 81, wherein the desired percent coverage by the infusate in the target putamen is from about 40% to about 90% of the target putaminal volume ($Vp_{(t)}$).

90. The computer-implemented method of claim 81, wherein the total infusion volume ($Vi_{(T)}$) of the infusate includes a first infusion volume ($Vi_{1(t)}$), a second infusion volume ($Vi_{2(t)}$), and a third infusion volume ($Vi_{3(t)}$).

91. The computer-implemented method of claim 90, wherein the first infusion volume ($Vi_{1(t)}$) is from about 10% to about 30% of the total infusion volume ($Vi_{(T)}$), the second infusion volume ($Vi_{2(t)}$) is from about 30% to about 50% of the total infusion volume ($Vi_{(T)}$), and the third infusion volume ($Vi_{3(t)}$) is from about 30% to about 50% of the total infusion volume ($Vi_{(T)}$).

92. The computer-implemented method of claim 91, wherein the first infusion volume ($Vi_{1(t)}$) is from about 15% to about 25% of the total infusion volume ($Vi_{(T)}$), the second infusion volume ($Vi_{2(t)}$) is from about 35% to about 40% of the total infusion volume ($Vi_{(T)}$), and the third infusion volume ($Vi_{3(t)}$) is from about 40% to about 45% of the total infusion volume ($Vi_{(T)}$).

93. The computer-implemented method of claim 91, wherein the first infusion volume ($Vi_{1(t)}$) is calculated to be delivered to a posterior segmental region of the target putamen, the second infusion volume ($Vi_{2(t)}$) is calculated to be delivered to a middle segmental region of the target putamen, and the third infusion volume ($Vi_{3(t)}$) is calculated to be delivered to an anterior segmental region of the target putamen.

94. The computer-implemented method of claim 93, further comprising infusing the infusion volume of the infusate via the cannula, the infusing including simultaneous infusion of the infusate in a posterior segmental region of the target putamen, a middle segmental region of the target putamen, and an anterior segmental region of the target putamen.

95. The computer-implemented method of claim 81, wherein the determining of the sample putaminal volumes ($Vp_{(s)}$) from a set of sample subjects is performed by scanning each putamen of each of the set of sample subjects via a scanner, the scanner is a magnetic resonance imaging (MRI) scanner.

96. The computer-implemented method of claim 81, wherein the sample volume of distribution ($Vd_{(s)}$) for each sample putamen is determined by a magnetic resonance imaging (MRI) scanner.

97. The computer-implemented method of claim 81, further comprising verifying the total infusion volume ($Vi_{(T)}$) of the infusate with a desired clinical outcome for a therapeutic agent in the infusate.

98. The computer-implemented method of claim 97, wherein the desired clinical outcome is an improvement identified during a treatment of a central nervous system (CNS) disorder.

99. A system for determining a first infusion volume ($Vi_{1(t)}$), a second infusion volume ($Vi_{2(t)}$), and a third infusion volume ($Vi_{3(t)}$) of an infusate to infuse into a first target segmental region, a second target segmental region, and a third target segmental region of a subject's target putamen having only three target segmental regions, respectively, in order to achieve a desired percent coverage of the infusate of at least about 40% of the target putamen in the subject, the system comprising:

an input interface to receive data on a target putaminal volume ($Vp_{(t)}$) of the target putamen measured by MRI, a number of the plurality of target segmental regions of the target putamen, and the desired percent coverage;

a storage device storing for each of a plurality of sample putamina:

(1) sample putaminal volumes ($Vp_{(s)}$) obtained from sample putamina from a set of sample subjects, each sample putamen having a first sample segmental region, a second sample segmental region, and a third sample segmental region;

(2) first sample infusion volumes ($Vi_{1(s)}$) of the infusate individually infused into each first sample segmental region, second sample infusion volumes ($Vi_{2(s)}$) of the infusate individually infused into each second sample segmental region, and third sample infusion volumes ($Vi_{3(s)}$) of the infusate individually infused into each third sample segmental region, wherein a sum of the first, second, and third sample infusion volumes is a total sample infusion volume ($Vi_{1(s)} + Vi_{2(s)} + Vi_{3(s)} = Vi_{T(s)}$);

(3) sample volumes of distribution ($Vd_{(s)}$) of the infusate for each putamen, each sample volume of distribution ($Vd_{(s)}$) being a volume of the total sample infusion volume ($Vi_{T(s)}$) retained within each sample putamen; and

(4) a sample percent coverage for the infusate in each sample putamen, each sample percent coverage calculated by dividing each sample volume of distribution ($Vd_{(s)}$) by the corresponding sample putaminal volume ($Vp_{(s)}$);

a processor coupled to the input interface and the storage device, the processor configured to determine the total infusion volume ($Vi_{(T)}$) of the infusate to infuse into the target putamen and the first, second, and third infusion volumes ($Vi_{1(t)} + Vi_{2(t)} + Vi_{3(t)} = Vi_{(T)}$) to infuse into each target segmental region of the target putamen based on:

(a) the desired percent coverage;

(b) the first, second, and third target segmental regions of the target putamen;

(c) the target putaminal volume ($Vp_{(t)}$); and

(d) a plurality of stored sample data selected from the following: the sample putaminal volumes ($Vp_{(s)}$), the first, second, and third sample segmental regions per

sample putamen, the first, second, and third sample infusion volumes ($Vi_{(s)}$), the total sample infusion volumes ($Vi_{(T)}$), the sample volumes of distribution ($Vd_{(s)}$), and the sample percent coverages; and

an output interface providing the total infusion volume ($Vi_{(T)}$) of the infusate to administer to the target putamen and the first, second, and third infusion volumes ($Vi_{1(t)}$, $Vi_{2(t)}$, $Vi_{3(t)}$) to administer to the first, second, and third target segmental regions, respectively, to achieve the desired percent coverage of the infusate, wherein the first infusion volume ($Vi_{1(t)}$) is from about 10% to about 30% of the total infusion volume ($Vi_{(T)}$), the second infusion volume ($Vi_{2(t)}$) is from about 30% to about 50% of the total infusion volume ($Vi_{(T)}$), and the third infusion volume ($Vi_{3(t)}$) is from about 30% to about 50% of the total infusion volume ($Vi_{(T)}$).

100. The system of claim 99, wherein the first infusion volume ($Vi_{1(t)}$) is from about 15% to about 25% of the total infusion volume ($Vi_{(T)}$), the second infusion volume ($Vi_{2(T)}$) is from about 35% to about 40% of the total infusion volume ($Vi_{(T)}$), and the third infusion volume ($Vi_{3(T)}$) is from about 40% to about 45% of the total infusion volume ($Vi_{(T)}$).

101. The system of claim 100, wherein the first infusion volume ($Vi_{1(T)}$) is about 20% of the total infusion volume ($Vi_{(T)}$), the second infusion volume ($V_{2(T)}$) is about 37% of the total infusion volume ($Vi_{(T)}$), and the third infusion volume ($Vi_{3(T)}$) is about 43% of the total infusion volume ($Vi_{(T)}$).

102. The system of claim 99, wherein a first target segmental region of the target putamen, a second target segmental region of the target putamen, and a third target segmental region of the target putamen correspond to the first sample segmental region of the sample putamen, the second sample segmental region of the sample putamen, and the third sample segmental region of the sample putamina, respectively.

103. The system of claim 102, wherein the first target segmental region of the target putamen is a posterior segmental region of the target putamen, a second target segmental region of the target putamen is a middle segmental region of the target putamen, and a third target segmental region of a target putamen is an anterior segmental region of the target putamen.

104. The system of claim 102, wherein the first infusion volume ($Vi_{1(T)}$) is to be delivered to the posterior segmental region of the target putamen, the second infusion volume ($Vi_{2(T)}$) is to be delivered to a middle segmental region of the target putamen, and the third infusion volume ($Vi_{3(T)}$) is to be delivered to an anterior segmental region of the target putamen.

105. A method of implementing a total infusion volume ($Vi_{(t)}$) of an infusate into a target putamen of a subject in need thereof to achieve an infusate coverage of at least 40% in the target putamen, the method comprising:

providing a distance from a posterior end of the target putamen to an anterior end of the target putamen, the distance being along a longitudinal axis of the target putamen;

determining locations of a predetermined number of a plurality of infusion sites along the longitudinal axis based on the distance;

providing the total infusion volume ($Vi_{(t)}$) of the infusate to be infused into the target putamen, the total infusion volume being greater than 1000 μL;

determining a plurality of segmental infusion volumes, each segmental infusion volume of the plurality to be infused into a corresponding infusion site being selected from the plurality of infusion sites, a sum of the plurality of segmental infusion volumes being the total infusion volume ($Vi_{(t)}$);

inserting a cannula through a brain of the subject and positioning the cannula in the target putamen; and

infusing each of the plurality of segmental infusion volumes of the infusate into each of the corresponding plurality of infusion sites of the target putamen.

106. The method of claim 105, wherein determining the plurality of segmental infusion volumes is based on a database derived from sample segmental infusion volumes infused into sample infusion sites of sample putamens resulting in sample coverages.

107. The method of claim 105, further comprising verifying accurate placement of the cannula in the target putamen using intraoperative computed tomography (CT).

108. The method of claim 105, further comprising:

infusing a first segmental infusion volume ($Vi_{(1)}$) of the infusate into a first infusion site;

advancing a distal end of the cannula to a second infusion site and infusing a second segmental infusion volume ($Vi_{(2)}$) of the infusate into the second infusion site; and

repeating the advancing and infusion steps until each of the plurality of infusion sites has been infused with the infusate.

109. The method of claim 105, further comprising:

infusing a first segmental infusion volume ($Vi_{(1)}$) of the infusate into the first infusion site;

advancing a distal end of the cannula to a second infusion site and infusing a second segmental infusion volume ($Vi_{(2)}$) of the infusate into the second infusion site; and

advancing the distal end of the cannula to a third infusion site and infusing a third segmental infusion volume ($Vi_{(3)}$) of the infusate into the third infusion site.

110. The method of claim 109, further comprising:

advancing the distal end of the cannula to a fourth infusion site and infusing a fourth segmental infusion volume ($Vi_{(4)}$) of the infusate into the fourth infusion site.

111. The method of claim 105, wherein the infusate coverage by the infusate in the target putamen is from about 40% to about 90% of the volume of the target putamen of the subject.

112. The method of claim 111, wherein the infusate coverage by the infusate in the target putamen is from about 50% to about 80% of the volume of the target putamen of the subject.

113. The method of claim 105, wherein the infusing is performed with a syringe pump.

114. The method of claim 105, wherein the infusion occurs only at the plurality of infusion sites.

115. The method of claim 105, wherein the cannula comprises a stylet and further including removing the stylet without removing the cannula from the target putamen of the subject.

116. The method of claim 105, further including measuring the infusate coverage by the infusate in the target putamen after the total infusion volume ($Vi_{(T)}$) of the infusate has been infused.

117. The method of claim 116, wherein the measuring of the infusate coverage is performed using MRI.

118. The method of claim 105, wherein the total infusion volume ($Vi_{(T)}$) delivered to the target putamen is greater than 1200μL.

119. The method of claim 118, wherein the total infusion volume ($Vi_{(T)}$) delivered to the target putamen is greater than 1400μL.

120. The method of claim 105, wherein the total infusion volume ($Vi_{(T)}$) delivered to the target putamen is from about 1,000 to about 2,000μL.

121. The method of claim 120, wherein the total infusion volume ($Vi_{(T)}$) delivered to the target putamen is from about 1,300 to about 1,800μL.

122. The method of claim 105, wherein the infusate is infused to the plurality of infusion sites at a rate of from about 2 to about 12 μL/min.

123. The method of claim 122, wherein the rate is from about 3 to about 10 μL/min.

124. The method of claim 105, wherein the predetermined number of the plurality of infusion sites is 4, and where:

a first infusion site is from 3 mm to 8 mm from the posterior end of the target putamen;

a fourth infusion site is from 5 mm to 15 mm from the anterior end of the target putamen; and

a second infusion site and a third infusion site are 1/3 and 2/3 of a distance between the first and fourth infusion sites, respectively.

125. The method of claim 124, wherein the plurality of segmental infusion volumes is 4 infusion volumes, each of the 4 infusion volumes to be infused into one of the 4 infusion sites, and wherein:

a first segmental infusion volume is from 5% to 20% of the total infusion volume;

a second segmental infusion volume is from 25% to 35% of the total infusion volume;

a third segmental infusion volume is from 25% to 35% of the total infusion volume; and

a fourth segmental infusion volume is from 10% to 30% of the total infusion volume.

126. The method of claim 125, comprising:

infusing the first segmental infusion volume of the infusate into the first infusion site;

infusing the second segmental infusion volume of the infusate into the second infusion site;

infusing the third segmental infusion volume of the infusate into the third infusion site; and

infusing the fourth segmental infusion volume of the infusate into the fourth infusion site.

127. The method of claim 126, wherein the total infusion volume is about 1500 μL, the first segmental infusion volume is about 150 μL, the second segmental infusion volume is about 500 μL; the third segmental infusion volume is about 500 μL; and the fourth segmental infusion volume is about 350 μL.

128. The method of claim 127, wherein the cannula is positioned using preoperative imaging scans and without real-time MRI guidance.

129. A method of implementing a total infusion volume ($Vi_{(t)}$) of an infusate into a target putamen of a subject in need thereof to achieve a therapeutically effective coverage of the infusate in the target putamen, the method comprising:

providing a distance from a posterior end of the target putamen to an anterior end of the target putamen, the distance being along a longitudinal axis of the target putamen;

determining locations of at least three infusion sites along the longitudinal axis based on the distance,

a first of the at least three infusion sites being from 3 mm to 8 mm from the posterior end of the target putamen;

a last of the at least three infusion sites being from 5 mm to 15 mm from the anterior end of the target putamen; and

a remainder of the infusion sites being about equally spaced between the first and last infusion sites;

providing the total infusion volume ($Vi_{(t)}$) of the infusate to be infused into the target putamen, the total infusion volume being greater than 1000 μL;

determining at least three segmental infusion volumes to be independently infused into each of the at least three infusion sites, a sum of the segmental infusion volumes being the total infusion volume ($Vi_{(t)}$); and

infusing the at least three segmental infusion volumes of the infusate individually into the at least three infusion sites of the target putamen.

130. The method of claim 129, wherein the infusing comprises:

positioning a distal end of a cannula at the first one of the at least three infusion sites and infusing a first of the at least three segmental infusion volume of the infusate into the first of the at least three infusion sites;

advancing the distal end of the cannula to a second of the least three infusion sites and infusing a second of the at least three segmental infusion volumes of the infusate into the second of the at least three infusion sites; and

repeating the advancing and the infusing until a last of the at least three segmental infusion volumes of the infusate has been infused into the last of the at least three infusion sites.

131. The method of claim 129, wherein determining the at least three segmental infusion volumes is based on a database derived from sample segmental infusion volumes infused into sample infusion sites of sample putamens resulting in sample coverages.

132. The method of claim 129, wherein the determining locations of at least three infusion sites comprises determining locations of only a first infusion site, a second infusion site, and a third infusion site, the first infusion site being the first of the least three infusion sites, the third infusion site being the last of the at least three infusion sites, and the second infusion site being about midway between the first and the third infusion sites.

133. The method of claim 132, wherein the determining the least three segmental infusion volumes comprises determining a first segmental infusion volume to be infused into the first infusion site, a second segmental infusion volume to be infused into the second infusion site, and a third segmental infusion volume to be infused into the third infusion site, and wherein:

the first segmental infusion volume is 5-40% of the total infusion volume;

the second segmental infusion volume is 33-80% of the total infusion volume; and

the third segmental infusion volume is 7-47% of the total infusion volume.

134. The method of claim 129, wherein the determining locations of at least three infusion sites comprises determining locations of only a first infusion site, a second infusion site, a third infusion site, and a fourth infusion site, the first infusion site being the first of the least three infusion sites, the fourth infusion site being the last of the at least three infusion sites, and the second and third infusion sites being about 1/3 and about 2/3 of the distance between the first and fourth infusion sites, respectively.

135. The method of claim 134, wherein the determining the least three segmental infusion volumes comprises determining a first segmental infusion volume to be infused into the first infusion site, a second segmental infusion volume to be infused into the second infusion site, a third segmental infusion volume to be infused into the third infusion site, and a fourth segmental infusion volume to be infused into the fourth infusion site, and wherein:

the first segmental infusion volume is from 2% to 27% of the total infusion volume;

the second segmental infusion volume is from 20% to 47% of the total infusion volume;

the third segmental infusion volume is from 20% to 47% of the total infusion volume; and

the fourth segmental infusion volume is from 7% to 40% of the total infusion volume.

136. The method of claim 129, wherein the determining locations of at least three infusion sites comprises determining locations of only a first infusion site, a second infusion site, a third infusion site, a fourth infusion site, and a fifth infusion site, the first infusion site being the first of the least three infusion sites, the fifth infusion site being the last of the at least three infusion sites, and the second, third, and fourth infusion sites being about ¼, about ½, and about ¾ of the distance between the first and fifth infusion sites, respectively.

137. The method of claim 136, wherein the determining the least three segmental infusion volumes comprises determining a first segmental infusion volume to be infused into the first infusion site, a second segmental infusion volume to be infused into the second infusion site, a third segmental infusion volume to be infused into the third infusion site, a fourth segmental infusion volume to be infused into the fourth infusion site, and a fifth segmental infusion volume to be infused into the fifth infusion site, and wherein:

the first segmental infusion volume is 2-27% of the total infusion volume;

the second segmental infusion volume is 3-23% of the total infusion volume;

the third segmental infusion volume is 20-47% of the total infusion volume;

the fourth segmental infusion volume is 10-37% of the total infusion volume; and

the fifth segmental infusion volume is 3-27% of the total infusion volume.

138. The method of claim 129, wherein the therapeutically effective coverage is greater than 40%.

139. A method of implementing a total infusion volume ($Vi_{(t)}$) of an infusate into a target putamen of a subject in need thereof to achieve an infusate coverage of at least 40% in the target putamen, the method comprising:

verifying the accuracy of the placement of the cannula in the absence of magnetic resonance imaging (MRI);

infusing a first segmental infusion volume of the infusate into a first infusion site using a cannula;

advancing a distal end of the cannula to a second infusion site and infusing a second segmental infusion volume of the infusate into the second infusion site;

advancing the distal end of the cannula to a third infusion site and infusing a third segmental infusion volume of the infusate into the third infusion site; and

advancing the distal end of the cannula to a fourth infusion site and infusing a fourth segmental infusion volume of the infusate into the fourth infusion site,

wherein the second and third infusion sites are located between the first and fourth infusion sites.

wherein the aggregate of the first segmental infusion volume, the second segmental infusion volume, the third segmental infusion volume, and the fourth segmental infusion volume is a total infusion volume delivered to the target putamen, the total infusion volume

($Vi_{(T)}$) being greater than 1,000μL, the first segmental infusion volume being from about 2 to about 27% of the total infusion volume, the second segmental infusion volume being from about 20 to about 47% of the total infusion volume, the third segmental infusion volume being from about 20 to about 47% of the total infusion volume, the fourth segmental infusion volume being from about 7 to about 40% of the total infusion volume.

140. The method of claim 139, wherein the infusate coverage by the infusate in the target putamen is from about 40% to about 90% of a volume of the target putamen of the subject.

141. The method of claim 140, wherein the infusate coverage by the infusate in the target putamen is from about 50% to about 80% of the volume of the target putamen of the subject.

142. The method of claim 139, wherein the total infusion volume delivered to the target putamen is from about 1,000μL to about 2,000μL.

143. The method of claim 142, wherein the total infusion volume delivered to the target putamen is from about 1,200μL to about 1,800μL.

144. The method of claim 143, wherein the total infusion volume delivered to the target putamen is from about 1,400μL to about 1,600μL.

145. The method of claim 139, wherein the first segmental infusion volume is from about 5 to about 25% of the total infusion volume ($Vi_{(T)}$), the second segmental infusion volume being from about 20 to about 40% of the total infusion volume, the third segmental infusion volume being from about 20 to about 40% of the total infusion volume, and the fourth segmental infusion volume being from about 10 to about 35% of the total infusion volume such that the percent coverage by the infusate in the target putamen is at least 50% of the volume of the target putamen of the subject.

146. The method of claim 145, wherein the first segmental infusion volume is from about 5 to about 25% of the total infusion volume ($Vi_{(T)}$), the second segmental infusion volume being from about 25 to about 35% of the total infusion volume, the third segmental infusion volume being from about 25 to about 35% of the total infusion volume, and the fourth segmental infusion volume being from about 10 to about 30% of the total infusion volume

such that the percent coverage by the infusate in the putamen is at least 50% of the volume of the target putamen of the subject.

147. The method of claim 139, wherein the first infusion site is located near a posterior end of the target putamen and the fourth infusion site is located near an anterior end of the target putamen, the second infusion site being located approximately equidistance between the first infusion site and the third infusion site, the third infusion site being located approximately equidistance between the second infusion site and the fourth infusion site.

148. The method of claim139, wherein the first infusion site is from about 3 to about 8mm from the posterior end of the target putamen, and the fourth infusion site is from about 5 to about 15mm from the anterior end of the target putamen.

149. The method of claim 139, wherein the first segmental infusion volume, the second segmental infusion volume, the third segmental infusion volume, and the fourth segmental infusion volume are infused sequentially.

150. The method of claim 139, wherein the cannula comprises a stylet and further including removing the stylet without removing the cannula from the target putamen of the subject.

151. The method of claim 139, further including measuring the infusate coverage by the infusate in the target putamen after the total infusion volume ($Vi_{(t)}$) of the infusate has been infused.

152. The method of claim 139, wherein a rate of the infusate to the target infusion sites of the target putamen is from about 2 to about 12 μL/min.