

SYSTEMS AND METHODS FOR AN INTRANASAL DRUG DELIVERY SYSTEM

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This is an International Patent Application claiming priority to and the benefit of US Provisional Patent Application No. 63/283,150, filed 24 November 2021, which is incorporated by reference herein in its entirety.

TECHNICAL FIELD

[0002] The present disclosure relates generally to systems and methods for improving mental health and/or performance using an intranasally-administered neuron editing drug.

BACKGROUND

[0003] The nasal pathway may represent a non-invasive administration route for active biopharmaceutical ingredients for local, systemic and central nervous system (CNS) action. Although the nasal epithelium appears to function as a tight barrier, the tightness of the intercellular junctional complex of the nasal mucosa may often be low due to leaky epithelial tissue. In addition, the extensive vascularization of the mucosa and lamina propria provide an optimal absorption surface for delivery of molecular therapies. The direct absorption of molecules through the trigeminal and olfactory pathways from the nasal cavity provides a direct entrance to the brain and may result in beneficial pharmacokinetic and pharmacodynamics profiles for CNS acting biologics. This route of administration is a promising new pathway for dosing highly potent and efficacious CNS-targeted biologics to reach the brain parenchyma by bypassing the blood-brain barrier. However, untargeted manipulation of CNS acting biologics via RNA or DNA affects the whole brain, potentially causing unwanted side effects and/or canceling out the desired effects.

For example, although conventional forms of CRISPR can distinguish neurons from other types of cells in the body, they cannot differentiate between various areas in the brain.

[0004] As a result, improved methods of delivering CNS acting biologics which target specific areas of the brain are needed.

SUMMARY

[0005] One aspect of the present disclosure includes methods of treating a patient with a mental health condition. These methods include administering a dose of a neuron-editing biologic intranasally to the patient. Such methods may also include administering a brain region activator to activate a target brain region for treatment. These methods further include transporting the neuron-editing biologic to active neurons within the target brain region using hemodynamics. The neuron-editing biologics may then normalize brain activity within the target brain region.

[0006] Another aspect of the present disclosure relates to methods of improving a patient's cognitive capacity. Such methods include administering a dose of a neuron-editing biologic intranasally to the patient. These methods also include administering a brain region activator to activate a target brain region. The methods further include transporting the neuron-editing biologic to the active neurons within the target brain region using hemodynamics. The neuron-editing biologics may then improve and/or enhance brain activity within the target brain region.

[0007] The foregoing has outlined rather broadly several features and technical advantages of examples of this disclosure so that the detailed description that follows may be better understood. Additional features and advantages will be described hereinafter. The concepts and specific examples disclosed herein may be readily utilized as a basis for modifying or designing other methods, constructs and/or systems for carrying out the same or similar purposes of the

present disclosure. Such equivalent constructions do not depart from the spirit and scope of the appended claims. Features which are believed to be characteristic of the concepts disclosed herein, both as to their organization and method of operation, together with associated advantages will be better understood from the following description when considered in connection with the accompanying figures. Each of the figures is provided for the purpose of illustration and description only, and not as a definition of the limits of the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] A further understanding of the nature and advantages of the embodiments may be realized by reference to the following drawings. In the appended figures, similar components or features may have the same reference label.

[0009] FIG. 1 is a diagram listing a variety of neuron editing biologics in accordance with the principles of the present disclosure.

[0010] FIG. 2 is a diagram listing a variety of brain region activators in accordance with the principles of the present disclosure.

[0011] FIGS. 3A, 3B, 4A, and 4B illustrate an exemplary method of delivering a neuron-editing biologic drug intranasally in accordance with the present disclosure.

[0012] FIG. 5 illustrates the structure of a neuron-editing biologic, and its manufacture into a delivery form (via insertion into an AAV or other vector) to facilitate intranasal delivery in accordance with the present disclosure.

[0013] FIG. 6 illustrates an example transparent polycarbonate cages used as part of the experimental setup in Example 1 of the present disclosure below.

[0014] FIG. 7 illustrates a bar graph of the results of Example 1 in accordance with the present disclosure.

[0015] FIG. 8 illustrates a stain of a portion of a brain of a mouse used an experiment recorded as Example 1 in accordance with the present disclosure.

[0016] FIGS. 9A, 9B, 9C, and 9D illustrate stains of a portion of a brain of a mouse from Example 1 in accordance with the present disclosure.

[0017] FIGS. 10A, 10B, and 10C illustrate stains of a portion of a brain of a mouse used Example 1 in accordance with the present disclosure.

[0018] FIGS. 11A, 11B, and 11C illustrate stains of a portion of a brain of a mouse used in Example 1 in accordance with the present disclosure.

[0019] FIG. 12 illustrates the structure of a neuron-editing biologic to facilitate intranasal delivery in accordance with the present disclosure.

[0020] While the embodiments described herein are susceptible to various modifications and alternative forms, specific embodiments have been shown by way of example in the drawings and will be described in detail herein. However, the exemplary embodiments described herein are not intended to be limited to the particular forms disclosed. Rather, the instant disclosure covers all modifications, equivalents, and alternatives falling within the scope of the appended claims.

DETAILED DESCRIPTION

[0021] This description provides examples, and is not intended to limit the scope, applicability or configuration of the invention. Rather, the ensuing description will provide those skilled in the art with an enabling description for implementing embodiments of the invention. Various changes may be made in the function and arrangement of elements.

[0022] Thus, various embodiments may omit, substitute, or add various procedures or components as appropriate. For instance, it should be appreciated that the methods may be

performed in an order different than that described, and that various steps may be added, omitted or combined. Also, aspects and elements described with respect to certain embodiments may be combined in various other embodiments. It should also be appreciated that the following systems, methods, and devices may individually or collectively be components of a larger system, wherein other procedures may take precedence over or otherwise modify their application.

[0023] The detailed description of exemplary embodiments herein makes reference to the accompanying drawings, which show exemplary embodiments by way of illustration. While these exemplary embodiments are described in sufficient detail to enable those skilled in the art to practice the disclosure, it should be understood that other embodiments may be realized and that logical changes and adaptations in design and construction may be made in accordance with this disclosure and the teachings herein without departing from the spirit and scope of the disclosure. Thus, the detailed description herein is presented for purposes of illustration only and not of limitation.

[0024] As used herein, neuron editing biologics are biopharmaceuticals, in some cases protein-based, or peptide-based biopharmaceuticals, which can modify a neuron's DNA or RNA. Fig. 1 illustrates eight examples of neuron-editing biologics which are discussed below. As listed, these may include gene knockout biologics, gene silencing biologics, and/or gene knock-in biologics.

[0025] Gene knockout biologics may include a catalytically-active gene-editing endonuclease(s) complexed with a synthetic guide RNA. Gene silencing biologics may include a catalytically-inactive gene-editing endonuclease(s) complexed with a synthetic guide RNA. Gene knock-in biologics may include a gene-editing endonuclease(s) complexed with a gene-expression inhibiting nucleotide and a synthetic guide RNA.

[0026] As used herein, transcriptional engineering biologics may include RNA knockout, RNA silencing, RNA knock-in, RNA translational interference, and Micro-RNA biogenesis suppression compounds/systems. RNA knockout compounds may include a catalytically-active RNA-editing ribonuclease complexed with a single guide RNA to alter RNA nucleotides to repress gene translation. RNA silencing compounds may include is a catalytically-inactive RNA-editing ribonuclease complexed with a single guide RNA to bind to RNA nucleotides to repress or enhance gene translation. RNA knock-in biologic may include a catalytically-inactive RNA-editing ribonuclease complexed with a single guide RNA and a deaminase enzyme to cause RNA nucleobase substitutions which result in translational interference. RNA translational interference compounds may include an RNA-editing ribonuclease complexed with an RNA-expression inhibiting nucleotide and a single guide RNA to alter RNA nucleotides to cause translational interference. Micro-RNA biogenesis suppression compounds may include a catalytically-active ribonuclease complexed with a single guide RNA to alter nucleotides in biogenesis processing sites for micro-RNA used in the translation of genes in order to reduce their expression.

[0027] As used herein, brain region activators include methods and techniques for focusing and concentrating the neuronal activity in a patient's brain into a specific, targeted area of the brain. Fig. 2 lists six examples of brain region activators which are explained below. Others may be known to one skilled in the art.

[0028] As used herein, transcranial pulsed ultrasound is a technique which uses low-power, low-frequency ultrasound to stimulate high neuron activity in the brain. It may be directed to any brain region and precisely focused to areas as small as several cubic millimeters.

[0029] As used herein, transcranial magnetic stimulation is a form of neurostimulation which uses a shallow magnetic field to induce electric current to flow in small targeted regions near the surface of the brain.

[0030] As used herein, perceptual isolation is the deliberate removal of stimuli from the senses of a subject/patient. Examples of perceptual isolation methods include sleep masks, white noise, soundproofing, and/or floatation tanks.

[0031] As used herein, neurofeedback is a type of biofeedback that measures brain waves to produce a signal that can be used as feedback to teach self-regulation of brain function. Patients can be trained to alter their brain activity to increase performance on certain tasks, which in turn changes the signal and increases cerebral blood flow to a specified region of the brain.

[0032] As used herein, virtual reality may be an immersive, interactive, computer-generated experience which occurs in a simulated environment including auditory and visual feedback.

[0033] As used herein, psychotherapy is a wide field encompassing the use of any one or more of hundreds of different methods and techniques to improve an individual's well-being, behavior and mental health, including cognitive therapy and other forms of therapies.

[0034] Referring next to FIGS. 3A, 3B, 4A, and 4B, a flow diagram of a method 100 of delivering a drug intranasally is provided. Specifically, the diagram describes a method 100 for intranasally delivering gene therapies which modify neuron electrodynamic excitability in the brain's limbic region to treat common mental health issues such as stress, anxiety, depression, PTSD and ADD, as well as personality disorders. More specifically, as described herein, the method 100 enables a region of the patient's brain to be activated such that a drug delivered

intranasally can target the specific activated region of the brain to treat a specific mental health condition.

[0035] Common mental health issues such as stress, anxiety, depression and inattention are all experimentally correlated with overactive neurons in specific areas of the limbic system. Neuron activity levels in these areas can be normalized through gene therapies which alter a neuron's structure to lower its electrical excitability. Although conventional forms of CRISPR can distinguish neurons from other types of cells in the body, they cannot differentiate between various areas in the brain. The illustrated method 100 allows for delivery of neuron-editing biologics to targeted regions and connectomes of the brain to achieve specific neurological treatment or cognitive enhancement goals.

[0036] Directing CRISPR molecules to specific types of cells is known as vectoring. Current CRISPR vectoring technology can target neurons, but it cannot provide navigational specificity to individual areas within the brain. It is demonstrated herein, however, that biologics such as CRISPR biologics may be directed in a patient's bloodstream along with glucose and oxygen to specific active areas in the brain by the principles of hemodynamics.

[0037] Glucose and oxygen are the fuel which powers neuronal activity. The more active a neuron is, the faster it burns glucose and oxygen. Unlike other types of cells, neurons cannot store glucose, so their supply must be immediately replenished as soon as it is consumed. A circulatory system principle known as hemodynamics ensures the vital nutrients of glucose and oxygen are rapidly delivered to active neurons.

[0038] Hemodynamics principles can be used to direct CRISPR into active neurons which are firing. By employing a selective brain region activation process to concentrate the patient's neural activity into a targeted brain region, passive hemodynamics techniques can be used

to draw cerebral blood flow containing CRISPR neuron editing biologics into the region. By employing a selective brain region activation process to concentrate the patient's neural activity into a targeted brain region, the method 100 can use passive hemodynamics to draw cerebral blood flow containing CRISPR neuron editing biologics into the region. Additionally, ligand vectors may be used which include targeting peptide nanoparticles which can bind to receptors that are unique to different cell types and thus to deliver gene or transcriptional editing cargo to them.

[0039] A plurality of brain region activation processes can be used by cognitive neuroscience professionals to serve different applications and objectives. Method 100 outlines a framework and platform to enable cognitive neuroscience professionals to deploy a variety of applications that target specific regions of the brain to treat specific mental health conditions.

[0040] Generally, the method 100 generally includes the steps of (1) assessment of the patient/subject to determine issues and establish goals; (2) identification of brain regions to be treated; (3) pre-treatment/cognitive therapy of the patient; (4) prescription and administration of selected biologics to the patient; and (5) post-treatment/cognitive therapy.

[0041] In specific embodiments, the method 100 enables intranasal delivery of neuron-editing biologics to the olfactory epithelium via a swab or nasal inhaler. The olfactory bulb pathways transport the biologics directly to the limbic lobe and the neuron-editing biologics target the limbic system to treat mental health conditions such as, but not limited to, inattention, stress, anxiety and depression. In some instances, the method 100 may be used to attenuate hyperactive or hypoactive neurons in the limbic system which are responsible for inattention (ventral posterior cingulate cortex (PCC)), stress (amygdala, hippocampus), anxiety (amygdala), and depression (amygdala, hippocampus).

[0042] Advantages of method 100 include (1) limiting biologics delivery to the region of interest to minimize dosing requirements and avoid affecting other areas of the brain; (2) avoid damage to biologic agents by avoiding transit which would expose them to digestive enzymes or immune system response by delivering them intranasally; (3) alleviating hippocampal and amygdaloid hyperactivity or hypoactivity which may also improve memory and could potentially halt the progression of dementia and extend longevity; and (4) in addition to one-time DNA edits, some applications may involve multiple iterations of DNA edits. For example, the multiple iterations of DNA edits may include layered DNA edits, where the edit is divided into multiple smaller doses, or temporary RNA edits, which are repeated over time. Adeno-associated viral vectors have been used for editing neurons, but after one application, the body develops an immune response to the adeno-associated viral vectors, preventing further uses. However, using viral vectors for multiple iterations is feasible with intranasal delivery because it transports gene editing payloads directly into the brain without activating an immune system response.

[0043] Once inside the limbic lobe, the method 100 includes three further methods to direct neuron-editing biologics to a target region of the patient's brain. First, actively-directed hemodynamic vectoring can transport the biologics to specific areas of the patient's brain which are energized by brain region activators. Second, passive hemodynamic vectoring will naturally transport the biologics to the most active neurons of the patient's brain. Finally, ligand vectors including targeting peptide nanoparticles designed to direct editing biologics to neuron cell types may be used to direct them to specific brain regions of the patient's brain. Hemodynamic and ligand vectoring are complementary therapies. Ligand vectors may be pre-programmed to statically treat specific topographical areas of brainwave activity imbalance identified by a neuroimaging assessment. Hemodynamic vectors can dynamically treat in real-time systemic

electrophysiological activity imbalances stimulated, for example, by psychotherapy, virtual reality, and/or perceptual events, as well as statically targeting specific regions of the brain. However, ligand vectors can transport biologics only to neurons which have the receptor types of interest by sensing proteins which are unique to each receptor type, limiting the types of neurons that can be treated with ligand vectors. Method 100 enables biologics to edit any type of neuron by activating the neuron prior to intranasal delivery of the biologic, enabling the biologic to edit the types of neurons that ligand vectoring cannot edit.

[0044] Thus, method 100 may include a specific-purpose neurological condition reliever which works on individual conditions (e.g., inattention, stress, anxiety, depression) by genetically altering neuron structure in order to modify neuron electrodynamics. Method 100 relieves the conditions by intranasal delivery of neuron-editing biologics to the limbic system in combination with (1) actively-directed hemodynamic vectoring, (2) passive hemodynamic vectoring, and/or (3) ligand vectors.

[0045] Method 100 may include either or both of treatment 300 and enhancement 400 steps, as described in co-pending U.S. Patent Application No. 16/272,138, which is incorporated herein by reference. Treatment 300 generally includes treating a specific mental health condition and enhancement 400 generally includes general-purpose cognitive enhancements. Treatment 300 and enhancement 400 may be used together or separately as determined by a medical professional. Using the method 100, treatment 300, and enhancement 400 may be used to treat a variety of neurological medical conditions. Specifically, the method 100, including treatment 300, and enhancement 400 steps may be used to treat a wide variety of mental health conditions. In some specific instances, the method 100, treatment 300, and/or enhancement 400 steps may be used to treat Attention Deficit Disorder (ADD) and Attention Deficit Hyperactivity Disorder (ADHD),

Post Traumatic Stress Disorder (PTSD), Obsessive Compulsive Disorder (OCD), stress disorders, anxiety, depression, sleep conditions, memory conditions, personality disorders, schizophrenia, concussions and/or head injuries, Tourette Syndrome, psychosomatic issues, tinnitus, conscious awareness issues, inattention, mind wandering, cravings, mental focus issues, concentration issues, mindfulness issues, meditation issues, and intuition issues.

[0046] Treatment steps 300 may include treatment steps 301-317 that enable a medical professional to treat a mental illness such as ADD/ADHD, PTSD, OCD, stress disorders, anxiety, depression, sleep conditions, memory conditions, concussions and/or head injuries, Tourette Syndrome, psychosomatic issues, and/or tinnitus. However, before treatment 300 can begin, a medical professional prepares the patient with pre-treatment therapy. During pre-treatment therapy, the medical professional may set expectations which foster positive beliefs about change by employing psychological counseling techniques such as cognitive behavioral therapy, mindfulness-based stress reduction, neuro-linguistic programming, meditation, and/or visualization.

[0047] Treatment phase 300 may include step 301: a professional assessment to determine a condition to be treated. During step 301, a medical professional may conduct an assessment of the patient to identify a specific neurological issue, condition, and/or disorder to be treated. The medical professional can be a human or in some instances may be an AI computer program.

[0048] Treatment phase 300 may also include step 302: identification of brain regions affected by the identified neurological issue, condition, and/or disorder to be treated. Neurological conditions and disorders may cause under- or over-activation in multiple areas in the brain. The medical professional may order a neuroimaging study, such as, without limitation, an fMRI, PET

or SPECT brain scan, to pinpoint area(s) in the patient's brain which may be over- or under-activated. The brain scan may show abnormal activity in one or more regions, depending on the condition to be treated. Brain regions typically affected by 12 common neurological conditions are shown in Table 1 below.

[0049] Treatment phase 300 may further include step 303: selecting a brain region to be treated to improve the condition. The medical professional may establish treatment priorities according to the degree of over- or under-activation of each region as revealed in the neuroimaging study, in some instances beginning with the most over- or under-activated area.

[0050] Treatment phase 300 may further include step 304: selecting an appropriate brain region activator to activate the target brain regions. The brain region activator activates the selected brain region to be treated to enable the gene therapies to target the selected brain region. Specifically, the brain region activator is selected to activate a specific region of the brain such that the gene therapies are absorbed into the selected brain region. Table 1 illustrates 6 examples of brain region activators which may be suitable for any one or more of at least 12 neurological treatment applications. Other brain region activation methods can be devised and employed by those skilled in the art. The activator examples shown are: transcranial pulsed ultrasound (TPU), transcranial magnetic stimulation (TMS), neurofeedback, perceptual isolation, virtual reality (VR), and psychotherapy.

[0051] As briefly discussed above, TPU may involve the use of low intensity, low frequency ultrasound (LILFU) to stimulate the patient's brain and may be effective in a variety of applications because TPU can be focused in almost any area of the brain with a precision down to a few square millimeters. Furthermore, TPU may in some instances also increase the permeability of the brain's blood brain barrier, allowing for more effective transport of neuron-editing biologics

in the bloodstream to the target brain regions. TPU may also be used in combination with other tools and techniques such as, but not limited to, heat-sensitive CRISPR vectors, such as lipid nanoparticles, to provide very precise delivery targeting.

[0052] As also briefly discussed above, TMS may include a noninvasive form of brain stimulation in which a changing magnetic field is used to cause electric current at a specific area of the brain through electromagnetic induction and has been used successfully in the treatment of depression. However, TMS' effective range is maximal to neurons in the cortex, near the brain's surface with progressively less effect deep to the cortex. Neurofeedback is a technique involving the use of a type of biofeedback that presents real-time feedback from brain activity to a patient/subject in order to reinforce healthy brain function through operant conditioning and has been shown to be effective across a wide spectrum of applications. Given use of the appropriate techniques, neurofeedback can be used to selectively activate almost any area in the brain of a subject.

[0053] As defined above, perceptual isolation includes the deliberate reduction or removal of stimuli from one or more of the senses of a subject and may be used in applications addressing the default mode network (DMN) (posterior cingulate cortex, medial prefrontal cortex, angular gyrus) to quiesce neural activity in other areas of the brain and concentrate neural activity into the DMN.

[0054] VR may include simulating in whole or in part, an experience that can be similar to or completely different from the real world. In some instances, VR has been used in applications treating aversive memories. A VR simulation can be used to strongly reactivate the memory and using methods of the invention, genetic or transcriptional therapies can be used to attenuate the neuronal activity associated with the reactivated, unwanted memories.

[0055] Psychotherapy may include the use of psychological methods, particularly when based on regular personal interaction, to help a person change behavior, increase happiness, and/or overcome problems and can have efficacy in applications treating aversive memories, stress, anxiety, and/or depression. As discussed above, by reactivating unwanted memories or conditions, psychotherapy can be used with the methods of this disclosure to induce genetic or transcriptional therapies to attenuate their associated neuronal activity.

[0056] Treatment phase 300 may also include step 305: selecting a type of editing. According to methods provided herein, a medical professional may select a type of editing for treatment of the identified condition. For example, the medical professional may select one of at least transcriptional editing and genetic editing. Transcriptional editing may be used to produce a reversible, temporary result for testing purposes. Genetic editing is selected when the patient is ready for a permanent treatment.

[0057] Treatment phase 300 may further includes step 306: selecting a neuron-editing biologic. In some instances, the brain region selected for treatment may be over- or under-active. If the region is underactive, the medical professional may select neuron-editing biologics which raise neuron excitability to increase activity in the region. If the region is overactive, the medical professional may select neuron-editing biologics which reduce neuron excitability in order to lower neuronal circuitry in the region. In some methods, a neuron's excitability can be reduced by decreasing its receptor population. One method for decreasing the receptor population is to edit gene HTR2A or its transcriptional or translational pathways to reduce HTR2A's expression, thus lowering the population of serotonin 2A receptors, as described in co-pending U.S. Patent Application No. 15/970,037, which is incorporated herein by reference. If ligand vectoring is to

be used, the medical professional selects neuron-editing biologics with ligand vectors targeting the brain area to be edited.

[0058] Treatment phase 300 may also include step 307: calculating a dosage of neuron-editing biologics for the selected brain region. In this step, the medical professional may calculate an appropriate dose based on a plurality of factors including, but not limited to, the age, weight, gender, and/or physical condition of the patient, the condition to be treated, and/or the region of the patient's brain to be targeted. An example of a dosing formula is included in co-pending U.S. Patent Application No. 15/970,037, which is incorporated herein by reference. If ligand vectoring is being used in the method, steps 308 and 309 of the treatment phase may be omitted, and a practitioner may instead proceed to step 310 described below.

[0059] Treatment phase 300 may further include step 308: calibrating the brain region activator. The medical professional calibrates the brain region activator method chosen in Step 304 discussed above to address the individual patient's brain region targeted for treatment. For transcranial pulsed ultrasound or transcranial magnetic stimulation, for example, the medical professional focuses the device on the target area in the patient's brain. For neurofeedback, the medical professional selects a neurofeedback program designed to address the patient's target brain region specifically. For perceptual isolation, the medical professional may select the stimuli reduction method to be used. For virtual reality, the medical professional may choose a VR simulation designed to evoke a particular memory or emotion related to the patient's issue. For psychotherapy, the medical professional may select a session protocol designed to evoke the patient's unwanted memory or condition.

[0060] The treatment phase 300 may also include step 309: quiesce brain activity. In this step, the patient may be placed in a resting state free from distractions to minimize brain activity to minimize activity in and/or deactivate all brain regions except the default mode network.

[0061] Treatment phase 300 may further include step 310: administering the calculated dose of the neuron-editing biologics to the subject. In this step, the neuron-editing biologics may be administered intranasally to the patient via swab or nasal inhaler.

[0062] If ligand vectors are being used, steps 311-313 may be omitted and a practitioner may instead proceed to step 314 described below.

[0063] Treatment phase 300 may also include step 311: administering the selected brain region activator to activate the target brain region(s). In this step, the medical professional administers the brain region activator method selected for the patient in Step 304 discussed in detail above.

[0064] Treatment phase 300 may further include step 312: concentrating neural activity in the target brain region using the brain region activator. The brain region activator is used by the practitioner to concentrate neuronal activity in the target brain region(s) of the patient/subject receiving treatment.

[0065] Treatment phase 300 may also include step 313: transporting the neuron-editing biologics to the active neurons within the target brain region using hemodynamics. As discussed above, cerebral blood flow containing glucose, oxygen, and neuron editing biologics is transported to active neurons in the targeted area of the patient's brain by hemodynamics principles.

[0066] Treatment phase 300 may further include step 314: editing the active neurons using the neuron-editing biologics. Neuron-editing biologics may here be used to transfect neurons

in the target area of the patient's brain and edit the neurons' DNA or RNA to normalize activity in the region as determined by the medical professional in the previous steps.

[0067] Treatment phase 300 may also include step 315: reducing symptoms of the condition. Normalized brain region activity relieves the symptoms of the patient's neurological condition.

[0068] Treatment phase 300 may further include step 316: iterating steps 302-315 as needed. If multiple brain areas are indicated for treatment, the medical professional may return to step 302 discussed above to address the next area of priority. The brain scan performed at this juncture may be used to verify/assess the potentially normalized brain activity in the region just treated.

[0069] Treatment phase 300 may also include step 317: conducting post-treatment therapy. Post-treatment therapy may be used to instill appropriate mind and life practices in the subject to reinforce the gene therapy's effects by fostering supportive behavioral and epigenetic factors. Post-treatment therapy can employ psychological counseling protocols such as cognitive behavioral therapy, mindfulness-based stress reduction, neuro-linguistic programming, meditation, visualization, and/or other techniques.

[0070] Table 1 illustrates the practical application of the treatment 300 in treating twelve examples of common neurological conditions:

Treatment								
		Brain region activator						
Issue	Main Brain regions affected	Change activity	Transcranial ultrasound	Transcranial magnetic stim.	Neurofeedback	Perceptual isolation	Virtual reality	Psychotherapy
1. ADD / ADHD	Amygdala, ventromedial prefrontal cortex, hippocampus (under-activated)	↑	•		•			
	Dorsal attention and default mode networks (over-activated)	↓	•		•	•		
2. Traumatic memory / PTSD	Amygdala, hippocampus	↓	•		•		•	•
	Ventromedial prefrontal cortex	↑	•		•		•	•
3. OCD	Orbital gyrus, caudate nucleus, dorsal anterior cingulate cortex	↓	•		•			
4. Stress disorders	Amygdala, hypothalamus	↓	•		•			•
5. Anxiety	Amygdala	↓	•		•			•
6. Depression	Posterior cingulate cortex, prefrontal cortex (underactive)	↑	•	•	•	•		
	Amygdala, hippocampus, anterior cingulate cortex (overactive)	↓	•		•			
7. Sleep issues	Prefrontal and parietal cortex, precuneus, anterior cingulate, mesial temporal, thalamus and hypothalamic arousal centers, default-mode network	↓	•		•	•		
8. Memory concerns	Hippocampus, amygdala	↑	•		•			
9. Concussions	Frontal and temporal lobes	↑	•		•			
10. Tourette Syndrome	Basal ganglia	↓	•					
11. Psychosomatic issues	Amygdala, hippocampus	↓	•		•			•
	Ventromedial prefrontal cortex	↑	•		•			•
12. Tinnitus	Auditory cortex	↓	•					

Table 1: practical applications of the treatment phase 300 of the method 100 in treating twelve examples of common neurological conditions.

[0071] In applying the methods of this disclosure, a medical practitioner should be aware of the characteristics of the neurological and/or psychiatric condition being treated, and devise specific treatment phase 300 methodologies as discussed with respect to the twelve examples provided in Table 1 below:

[0072] First, Attention Deficit Disorder (ADD) and Attention Deficit Hyperactivity Disorder (ADHD) may involve altered activation of the amygdala, ventromedial prefrontal cortex and/or hippocampus, depending on the ADD or ADHD subtype. Activity in these areas can be corrected by administering neuron-editing biologics designed to alter neuron excitability, in conjunction with transcranial pulsed ultrasound or neurofeedback brain region activation techniques which direct the biologics to the amygdala, ventromedial prefrontal cortex and/or hippocampus via hemodynamic vectoring.

[0073] ADD and ADHD may also involve overactivation of the dorsal attention and default mode networks. Activity in these areas can be reduced by administering neuron-editing biologics designed to alter-neuron excitability in conjunction with transcranial pulsed ultrasound, neurofeedback and/or perceptual isolation brain region activation techniques which direct the biologics to the dorsal attention and/or default mode networks via hemodynamic vectoring.

[0074] In some subjects, Post-Traumatic Stress Disorder (PTSD) may involve overactivation of the amygdala and/or hippocampus. These areas can be corrected by administering neuron-editing biologics for altering neuron excitability in conjunction with transcranial pulsed ultrasound, neurofeedback, virtual reality or psychotherapy brain region activation techniques selected to direct the biologics to the amygdala and/or hippocampus via passive hemodynamic vectoring.

[0075] PTSD may also be characterized by altered activation of the ventromedial prefrontal cortex. Activity in this area can be corrected by neuron-editing biologics for changing neuron excitability in conjunction with transcranial pulsed ultrasound, neurofeedback, virtual reality and/or psychotherapy brain region activation techniques which direct the biologics to the ventromedial prefrontal cortex via hemodynamic vectoring.

[0076] Neuroimaging studies of people with Obsessive Compulsive Disorder (OCD) have revealed hyperactivity in the dorsal anterior cingulate cortex, orbital gyrus and caudate nucleus. Activity in these areas can be normalized by administering neuron-editing biologics for reducing neuron excitability, together with transcranial pulsed ultrasound or neurofeedback brain region activation techniques which direct the biologics to the dorsal anterior cingulate cortex, orbital gyrus and/or caudate nucleus via hemodynamic vectoring.

[0077] Individuals with stress disorders exhibit hyperactivity in the amygdala and hypothalamus. These areas can be brought into balance by administering neuron-editing biologics for altering neuron excitability, combined with transcranial pulsed ultrasound, neurofeedback or psychotherapy brain region activation techniques which direct the biologics to the amygdala and/or hypothalamus via hemodynamic vectoring.

[0078] Individuals experiencing anxiety exhibit hyperactivity in the amygdala, which can be normalized by administering neuron-editing biologics for altering neuron excitability, combined with transcranial pulsed ultrasound, neurofeedback or psychotherapy brain region activation techniques which direct the biologics to the amygdala via hemodynamic vectoring.

[0079] Depression involves disrupted activation of the posterior cingulate cortex and prefrontal cortex. Activity in these areas can be corrected by administering neuron-editing biologics designed to normalize neuron excitability, in conjunction with transcranial pulsed

ultrasound, transcranial magnetic stimulation, neurofeedback, and/or perceptual isolation brain region activation techniques which direct the biologics to the posterior cingulate cortex and/or prefrontal cortex via hemodynamic vectoring.

[0080] Depression is also associated with altered activation of the amygdala, hippocampus and anterior cingulate cortex. Activity in these areas can be normalized by administering neuron-editing biologics designed to changing neuron excitability, in conjunction with transcranial pulsed ultrasound or neurofeedback brain region activation techniques which direct the biologics to the amygdala, hippocampus, and/or anterior cingulate cortex via hemodynamic vectoring.

[0081] Insomnia and other sleep issues can involve altered activation of the prefrontal and parietal cortex, precuneus, anterior cingulate, mesial temporal, thalamus and hypothalamic arousal centers, and the default-mode network. Activity in these areas can be normalized by administering neuron-editing biologics for correcting neuron excitability, in conjunction with transcranial pulsed ultrasound, neurofeedback and/or perceptual isolation brain region activation techniques which direct the biologics to the prefrontal and parietal cortex, precuneus, anterior cingulate, mesial temporal, thalamus and hypothalamic arousal centers, and/or the default-mode network via hemodynamic vectoring.

[0082] Neuroimaging studies of individuals with memory problems reveal subnormal activity in the hippocampus and amygdala. These areas can be normalized by administering neuron-editing biologics for altering neuron excitability, in conjunction with transcranial pulsed ultrasound or neurofeedback brain region activation techniques which direct the biologics to the hippocampus and/or amygdala via hemodynamic vectoring.

[0083] Head injuries may pathologically change neuronal activity in the frontal and temporal lobes. Corrected activity in these areas can be promoted by administering neuron-editing biologics for increasing neuron excitability, together with transcranial pulsed ultrasound or neurofeedback brain region activation techniques which direct the biologics to the frontal and/or temporal lobes via hemodynamic vectoring.

[0084] Studies of individuals with Tourette Syndrome show abnormal activity in the basal ganglia. Activity can be normalized by administering neuron-editing biologics for increasing neuron excitability, along with transcranial pulsed ultrasound brain region activation techniques which direct the biologics to the basal ganglia via hemodynamic vectoring.

[0085] Psychosomatic issues may involve overactivation of the amygdala and hippocampus. These areas can be normalized by administering neuron-editing biologics for changing neuron excitability, in conjunction with transcranial pulsed ultrasound, neurofeedback, or psychotherapy brain region activation techniques which direct the biologics to the amygdala and/or hippocampus via hemodynamic vectoring.

[0086] Psychosomatic issues may also cause altered activation of the ventromedial prefrontal cortex. Activity in this area can be corrected by neuron-editing biologics for normalizing neuron excitability, in conjunction with transcranial pulsed ultrasound, neurofeedback, or psychotherapy brain region activation techniques which direct the biologics to the ventromedial prefrontal cortex via hemodynamic vectoring.

[0087] Tinnitus/persistent ringing in the ears is caused by an overactivated auditory connections. Activity can be reduced by administering neuron-editing biologics for decreasing neuron excitability, along with transcranial pulsed ultrasound brain region activation techniques which direct the biologics to the auditory cortex via hemodynamic vectoring.

[0088] The enhancement phase 400 of the methods 100 disclosed herein may include enhancement steps 401-417 that enable a medical professional to enhance a subject's cognition, including areas such as, without limitation, conscious awareness issues, inattention, mind wandering, cravings, mental focus issues, concentration issues, mindfulness issues, meditation issues, and/or intuition issues. As a typical initial step before the enhancement phase 400 is initiated, a medical professional prepares the patient with pre-treatment therapy. During this pre-treatment therapy, the medical professional may set expectations which foster positive beliefs about change by employing psychological counseling techniques such as cognitive behavioral therapy, mindfulness-based stress reduction, neuro-linguistic programming, meditation, and/or visualization.

[0089] Enhancement phase 400 may include step 401: professional psychological assessment to verify a patient's suitability for cognitive enhancement. General-purpose genetic cognitive enhancement is generally suitable for adults in sound mental and emotional health. As a result, during step 401, a medical professional may conduct a psychological assessment of the patient to screen out candidates who do not meet this criteria, such as, for example, individuals with alcohol or substance abuse, bipolar disorder, depression, schizophrenia or other psychological conditions or disorders. The assessment also ensures the candidate is not currently taking any drugs, medications or substances that could interfere with the normal, natural functioning of their brain; such as, for example, certain prescription drugs, alcohol, caffeine, nicotine, cannabis, nootropics, ginseng or other similar substances or herbal preparations. In some instances, the medical professional who conducts this step can be a human or an AI computer program.

[0090] Enhancement phase 400 may also include step 402: conduct a psychological assessment to determine the patient's cognitive goals. The medical professional may conduct a

psychological assessment to ascertain the patient's cognitive enhancement goals. This assessment may cover several topics, including the type of cognitive enhancement the patient desires and whether the cognitive upgrade is to be permanent or temporary.

[0091] Enhancement phase 400 may further include step 403: selecting a brain region to be treated to achieve the cognitive goals previously identified. Target brain regions for thirteen specific cognitive enhancement applications are illustrated in Table 2. Genetic or transcriptional engineering can be used to optimize neuron performance in these regions in order to achieve the patient's goals. Depending on the application, optimization may involve increasing or decreasing neuronal activity. If ligand vectors are being used, step 404 may be omitted, and a medical professional may instead proceed to step 405 described below.

[0092] Enhancement phase 400 may further include step 404: selecting an appropriate brain region activator to activate the target brain regions. The brain region activator activates the selected brain region to be treated to enable the gene therapies to target the selected brain region. Specifically, the brain region activator is specifically selected to activate a specific region of the brain such that the gene therapies are directed to and absorbed into the selected brain region. Table 2 illustrates six examples of brain region activators suitable for thirteen exemplary cognitive enhancement applications. Other brain region activation methods can be devised by those skilled in the art based on the teachings provided herein. The activator examples shown are identical to the ones described in Step 304 described above.

[0093] Enhancement phase 400 may also include step 405: selecting a type of editing. The medical professional may select a type of editing for treatment of the identified condition. For example, the medical professional may select one of at least transcriptional editing and genetic editing. Transcriptional editing may be used to produce a reversible, temporary result in a patient,

such as for testing purposes, allowing the patient and/or practitioner to evaluate the effects of the enhancement on a temporary basis. Genetic editing may be selected when the patient is ready for a permanent treatment.

[0094] Enhancement phase 400 may further include step 406: selecting a neuron-editing biologic. The brain region selected for enhancement may be over- or under-active. If the region is underactive, the medical professional may select neuron-editing biologics which raise or lower neuron excitability to normalize activity in the region. If the region is overactive, the medical professional may select neuron-editing biologics which reduce neuron excitability in order to normalize the region. For example, a neuron's excitability can be reduced by decreasing its receptor population, which raises its electrical resistance. One way decreasing the receptor population is to edit gene HTR2A or its transcriptional or translational pathways to reduce HTR2A's expression, which will lower the population of serotonin 2A receptors, as described in co-pending U.S. Patent Application No. 15/970,037, which is incorporated herein by reference. If ligand vectoring is to be used, the medical professional may select neuron-editing biologics with ligand vectors targeting the brain area to be edited.

[0095] Enhancement phase 400 may also include step 407: calculating a neuron-editing biologics dose for the selected brain region. The medical professional calculates an appropriate dose for the neuron-editing biologics based on a plurality of factors including, but not limited to, the age, weight, gender, and/or physical condition of the patient, the condition to be treated, and/or the region of the patient's brain to be targeted. An example of a dosing formula is included in co-pending U.S. Patent Application No. 15/970,037, which is incorporated herein by reference. If ligand vectoring is being used, skip steps 408 and 409 and proceed to step 410 described below.

[0096] Enhancement phase 400 may further include step 408: calibrating the brain region system specific connectome. The medical professional calibrates the brain region method selected in Step 404 to address the patient's targeted brain region. For transcranial pulsed ultrasound or transcranial magnetic stimulation, the medical professional may focus the device on the target area in the patient's brain. For neurofeedback, the medical professional selects a neurofeedback program designed to address the patient's target brain region. For perceptual isolation, the medical professional selects the stimuli reduction method to be used. For virtual reality, the medical professional chooses a VR simulation designed to evoke a particular memory or emotion related to the patient's issue. For psychotherapy, the medical professional selects a session protocol which evokes the patient's unwanted memory or condition.

[0097] Enhancement phase 400 may also include step 409: quiesce brain activity. The patient may be placed in a resting state free from distractions to minimize brain activity in an effort to deactivate all brain regions except the default mode network of the patient.

[0098] Enhancement phase 400 may further include step 410: administering the calculated dose of the neuron-editing biologics. The neuron-editing biologics are here administered intranasally to the patient via swab or nasal inhaler. If ligand vectors are being used in this step, a medical practitioner may skip steps 411-413 and instead proceed to step 414 as described below.

[0099] Enhancement phase 400 may also include step 411: administering the brain region activator to activate the target brain regions. The medical professional administers the brain region activator method selected for the patient in Step 404.

[00100] Enhancement phase 400 may further include step 412: concentrating neural activity in the target brain region using the brain region connectome method. The brain regional

connectome analysis concentrates neuronal activity in the target brain region(s) as discussed above.

[00101] Enhancement phase 400 may also include step 413: transporting the neuron-editing biologics to the active neurons within the target brain region using hemodynamics. Cerebral blood flow containing glucose, oxygen, and neuron editing biologics is transported to active neurons in the targeted area of the patient's brain, facilitating administration of the selected biologic to the appropriate area of the subject's brain.

[00102] Enhancement phase 400 may further include step 414: editing the active neurons using the neuron-editing biologics. Neuron-editing biologics transfect neurons in the target area of the patient's brain and edit the neurons' DNA or RNA to enhance activity in the region.

[00103] Enhancement phase 400 may also include step 415: enhancing the patient's cognitive capacity. Optimized brain region activity may operate to expand the patient's cognitive capacity as desired.

[00104] Enhancement phase 400 may further includes step 416: iterating steps 402-415 as needed. If multiple brain areas are indicated for treatment, the medical professional returns to Step 402 to address the next area of priority. The brain scan performed at this juncture verifies optimized brain activity in the region just treated.

[00105] Enhancement phase 400 may also include step 417: conducting post-treatment therapy. Post-treatment therapy may be used to teach/instill mind and life practices for reinforcing the gene therapy's effects into the subject by fostering supportive behavioral and epigenetic factors. This therapy can employ psychological counseling protocols such as cognitive behavioral therapy, mindfulness-based stress reduction, neuro-linguistic programming, meditation, visualization and other techniques.

[00106] Table 2 illustrates the practical application of the enhancement 400 in treating thirteen examples of common cognitive enhancements:

Objective	Enhancement					
	Brain Regions	Transcranial ultrasound	Transcranial magnetic stim.	Neurofeedback	Perceptual isolation	Virtual reality Psychotherapy
1. Raise conscious awareness	Posterior cingulate cortex (ventral)	•			•	
2. Decrease inattention		•			•	
3. Reduce mind-wandering		•			•	
4. Lower craving		•			•	
5. Sharpen mental focus		•			•	
6. Increase concentration		•			•	
7. Enhance mindfulness		•			•	
8. Improve meditation		•			•	
9. Increase intuition		•			•	
10. Improve ESP	Caudate	•				
11. Cognitive therapy for unwanted behaviors	Various					•
12. Cognitive therapy for desired behaviors	Various					•
13. Alleviate cognitive impairment symptoms	Posterior cingulate cortex	•			•	

Table 2: practical application of the enhancement 400 in treating thirteen examples of common cognitive enhancements

[00107] Table 2 lists several exemplary practical applications for achieving cognitive enhancement. Several of these such as objectives 1-9 include general-purpose cognitive enhancements: raising conscious awareness, decreasing inattention, lowering craving, sharpening mental focus, increasing concentration, and improving meditation. These cognitive enhancements 1-9 may be achieved by administering neuron-editing biologics for decreasing neuron excitability, along with transcranial pulsed ultrasound and/or perceptual isolation brain region activation

techniques which direct the biologics to the ventral posterior cingulate cortex (PCC) via hemodynamic vectoring. Reduced PCC activity has been experimentally correlated with increased attention, conscious awareness, mental acuity, clarity, focus, concentration, and mindfulness, and with reduced mind-wandering, inattention and cravings.

[00108] Regarding cognitive enhancement 10 listed in Table 2, studies have shown that individuals who can demonstrate extra-sensory perception (ESP). Patients who desire to raise their ESP abilities may benefit from administering neuron-editing biologics for increasing neuron excitability, along with transcranial pulsed ultrasound brain region activation techniques which direct the biologics to specific brain regions via hemodynamic vectoring. NB the ‘caudate’ region noted in the unpublished pilot study is actually the internal capsule/striatal bridges region

[00109] Regarding cognitive enhancement 11 listed in Table 2, psychotherapy session protocols can be designed to stimulate the underlying causes of the patient’s unwanted behavior, including attitudes, emotions, beliefs, expectations, and memories. This mental activity will generate brainwave and neural activity in corresponding areas in the patient’s brain. Neuron editing biologics administered for reducing neuron excitability may then be transported to these active areas via hemodynamic vectoring.

[00110] Regarding cognitive enhancement 12 listed in Table 2, psychotherapy session protocols and immersive multi-sensory VR programs can be designed to help the patient visualize and experience desired behaviors, including attitudes, feelings, beliefs, expectations, and assumptions. This mental activity will generate neural activity in corresponding areas in the patient’s brain. Neuron editing biologics administered for altering neuron excitability will be transported to these active areas via hemodynamic vectoring.

[00111] Regarding cognitive enhancement 13 listed in Table 2, mild cognitive impairment (MCI) may affect many different regions of the brain. It can be treated indirectly by administering a cognitive enhancement protocol to offset its effects. This protocol involves administering neuron-editing biologics for decreasing neuron excitability in the posterior cingulate cortex (PCC), in conjunction with transcranial pulsed ultrasound or perceptual isolation techniques which direct the biologics to the PCC via hemodynamic vectoring.

Example 1: Immunolabeling experiments examining Crispr/Cas9 and 5HT-2A receptor localization following treatment with AAV1 and AAV2 in mice for 5 weeks

[00112] Methods of the present disclosure were tested as disclosed in the following experiment and accompanying protocols described in detail below.

[00113] Specifically, the marble burying test is used to record the number of marbles buried by mice placed in a novel environment. Mice, which are placed individually in a cage, bury glass marbles that are present in the cage. This test has some predictive value for anti-depressant and/or anxiolytic drugs. It has been shown to be sensitive to benzodiazepines as these compounds reduce burying behavior when compared to vehicle-treated control mice, without inducing changes in locomotor activity.

[00114] As shown in Table 3 below, an AAV (serotype AAV9) carrying CRISPR reagents for reducing anxiety was administered as a single 20 μ L dose (10 μ l per nostril), with two separate treatments, 5 weeks before the trial. Vehicle (control) animal received 20 μ L of saline for each treatment. The test animals were two groups of 15 CD-1 mice (~20 -30 g). Thus, each test mouse received a total of 1.9×10^{11} viral particles. Additionally, vehicle animals received 20 μ L of saline for each treatment.

Gr. nr.	Description	n	Test compound route	Dosage volume	Time before trial
1	Vehicle	15	in	10µL/nostril	5 weeks
2	AAV CRISPR reagent	15	in	10µL/nostril	5 weeks

Table 3: Test Animals Used in the Marble Burying Test

[00115] The AAV vectors (shown in FIG. 12) were provided by the sponsor and was administered intranasally. The vehicle for the test substance was saline. The test formulations were provided as follows: 1. 5 times 100µL of AAV9-GFP at 2.5×10^{13} GC/ML; and 2. 5 times 100µL of AAV9-Mecp2-spCas9 at 1.9×10^{13} GC/ML. The test formulations were prepared as follows: 1. dilute the AAV9-GFP at 1.9×10^{13} GC/ML to have both AAVs at the same concentration; and 2. mix 100µL of AAV9-GFP at 1.9×10^{13} GC/ML with 100µL of AAV9-Mecp2-spCas9 at 1.9×10^{13} GC/ML and add 200µL of saline. In that solution each AAV is at 4.75×10^{12} GC/mL. As shown in FIG. 5, the neuron-editing biologic is a plasmid that is inserted into an AAV virus (AVV1 or AVV2) and may contain two kinds of vectors, Cas9 mRNA and sgRNA GFP RNA.

[00116] In this test, the number of marbles buried by mice placed in a novel environment is recorded. As shown in FIG. 6, the apparatus includes transparent polycarbonate cages 600 (30 cm x 18 cm x 19 cm) containing a 5 cm layer of fine sawdust bedding and 20 glass marbles 602 (diameter: 1.5 cm) spaced evenly along the walls of the cage.

[00117] The marble burying test was performed once on the fourth week after the treatment. At the implementation of the test, each animal was placed individually in the cage without food or water where it remained for a 20 min test session. On termination of the test session the animals were removed from the cage and the number of marbles buried in the sawdust was recorded by the experimenter.

[00118] Immediately after the test, 3 mice of each group were anaesthetized with 5% isoflurane oxygen mixture and were killed by decapitation. Then the brain was then extracted and immediately preserved in 4% formalin solution for 48 hours and was subsequently transferred to vials containing 1% formalin in PBS buffer.

[00119] The results are illustrated in FIG. 7: Bar Graph of the Number of Marbles Buried. As shown in FIG. 7, the control group buried approximately 17 marbles on average and the CRISPR/Cas9 group buried approximately 15-16 marbles on average indicating that the treated mice were less anxious. For statistical analysis, pairwise differences between experimental groups was assessed using a one-tailed student t-test.

[00120] Additionally, as shown in FIGS. 8-11C, the AAV CRISPR reagent appeared to target specific regions of the brains of the mice. For FIGS. 8-11C, the following markers were used: (1) green fluorescent protein (GFP) as a reporter gene and (2) CY3-red fluorescence. Regarding the GFP, the DNA sequence was part of the AAV2 vector together with the guide RNA strand. Any green labeling indicates transduction of the guide RNA sequence inside cells. The CY3-red fluorescence was obtained using a proven, specific antibody to the 5HT2A receptor.

[00121] As shown in FIGS. 8-11C, the general pattern of GFP staining included staining within the olfactory bulb, the cortex, and the subcortical areas with substantially less staining in the hippocampus. There was strong GFP staining in olfactory bulb neuronal cell bodies with 5HT-2A labeling more evident in apical dendrites. In contrast, there was minimum labeling of GFP in vehicle-treated animals. As shown in Table 4 below, the treated mice had significantly greater staining of GFP than the vehicle-treated mice.

Mouse ID	Number of Marbles Buried	Overall Staining
ID1 Vehicle	17	No staining of GFP; minimal staining of 5HT2A
ID2 Vehicle	14	No staining of GFP; minimal staining of 5HT2A
ID6 Vehicle	18	No staining of GFP; minimal staining of 5HT2A
ID8 Treated	15	Best overall staining of GFP
ID10 Treated	16	Weakest staining of three treated animals (OK in cortex but limited in olfactory bulb)
ID15 Treated	19	Similar staining to ID8, good staining in olfactory bulb

Table 4: Staining Results of the Marble Burying Test

[00122] The results indicate that Crispr/Cas9 can deliver neuron-editing biologics into the brain including olfactory bulb, cortex, hypothalamus and other subcortical areas with reduced delivery into the hippocampus. Moreover, GFP labeling appears to be neuronal specific as no glial staining was detected. GFP expression appears to be delegated to cell body with little staining detected in apical dendrites, which is expected. Strong 5HT-2A receptor staining occurred in apical dendrites and weaker labeling occurred within the cell body consistent with potential knockout of the 5HT-2A receptor and corresponding turn-over.

[00123] The foregoing description, for purpose of explanation, has been described with reference to specific embodiments. However, the illustrative discussions above are not intended to be exhaustive or to limit the invention to the precise forms disclosed. Many modifications and

variations are possible in view of the above teachings. The embodiments were chosen and described in order to best explain the principles of the present systems and methods and their practical applications, to thereby enable others skilled in the art to best utilize the present systems and methods and various embodiments with various modifications as may be suited to the particular use contemplated.

[00124] Unless otherwise noted, the terms "a" or "an," as used in the specification and claims, are to be construed as meaning "at least one of." In addition, for ease of use, the words "including" and "having," as used in the specification and claims, are interchangeable with and have the same meaning as the word "comprising." In addition, the term "based on" as used in the specification and the claims is to be construed as meaning "based at least upon."

CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating a patient with a mental health condition, the method comprising:

administering a dose of a neuron-editing biologic intranasally to the patient;

administering a brain region activator to activate a target brain region of the patient; and

transporting the neuron-editing biologic to active neurons within the activated target brain region using hemodynamics, wherein the neuron-editing biologics normalize brain activity within the target brain region.
2. The method of claim 1, further comprising editing the active neurons using the neuron-editing biologics.
3. The method of claim 1, further comprising concentrating neural activity in the target brain region using the brain region activator.
4. The method of claim 1, further comprising quiescing brain activity.
5. The method of claim 4, wherein quiescing brain activity comprises placing the patient in a resting state free from distractions to minimize brain activity to deactivate brain regions except the default mode network.
6. The method of claim 1, further comprising selecting a type of the neuron-editing biologics.
7. The method of claim 1, further comprising selecting an appropriate brain region connectome to activate or deactivate the target brain region.
8. The method of claim 1, further comprising selecting the target brain region to be treated to improve the mental health condition.

9. The method of claim 1, further comprising identify brain regions affected by the mental health condition to be treated as the target brain regions.
10. The method of claim 1, further comprising calibrating the brain region activator.
11. A method of improving a patient's cognitive capacity, the method comprising:
 - administering a dose of a neuron-editing biologics intranasally to the patient;
 - administering a brain region activator to activate a target brain region of the patient; and
 - transporting the neuron-editing biologics to active neurons within the activated target brain region using hemodynamics, wherein the neuron-editing biologics normalize brain activity within the target brain region.
12. The method of claim 11, further comprising editing the active neurons using the neuron-editing biologics.
13. The method of claim 11, further comprising concentrating neural activity in the target brain region using the brain region activator.
14. The method of claim 11, further comprising quiescing brain activity.
15. The method of claim 14, wherein quiescing brain activity comprises placing the patient in a resting state free from distractions to minimize brain activity to deactivate all brain regions except the default mode network.
16. The method of claim 11, further comprising selecting a type of the neuron-editing biologics.
17. The method of claim 11, further comprising selecting an appropriate brain region activator to activate the target brain region.
18. The method of claim 11, further comprising selecting the target brain region to be treated to achieve a cognitive goal of the patient.

19. The method of claim 11, further comprising calculating the dose of the neuron-editing biologics for the selected brain region.
20. The method of claim 11, further comprising calibrating the brain region connectome.