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| (54) Title: DEEP BRAIN STIMULATION METHOD (57) Abstract <p>Disclosed is a method for treating a conscious patient having impaired cognitive function. The method includes selecting a conscious patient having impaired cognitive function and applying electrical stimulation to at least a portion of the patient's intralaminar nuclei under conditions effective to relieve the patient's impaired cognitive function. A method for improving coordination of function across a patient's cortical regions is also described. The method includes applying electrical stimulation to two or more subdivisions of the patient's intralaminar nuclei. The two or more subdivisions of the patient's intralaminar nuclei modulate separates cortical regions. Using the methods of the present invention, patient suffering from impaired cognitive function can have at least a portion of the function restored, thus improving their quality of life and reducing societal costs.</p> | | |

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DEEP BRAIN STIMULATION METHOD

5 The present application claims the benefit of
U.S. Provisional Patent Application Serial No.
60/062,728, filed October 22, 1997.

FIELD OF THE INVENTION

10 The present invention relates generally to deep
brain electrical stimulation methods and, more
particularly, methods for treating conscious patients
having impaired cognitive function.

BACKGROUND OF THE INVENTION

15 Brain injuries which lead to impaired cognitive
function remain the least explored area for active
neurological intervention. Several clinical observations
20 suggest that mechanisms of plasticity are available to
the brain that might be harnessed for therapeutic
advantage for treating cognitive disorders. A
significant percentage, roughly 20%, of patients who
suffer severe brain damage remain conscious with
25 preserved capacity for memory, attention, intention, and
awareness. In many cases these patients fluctuate
dramatically (e.g., the well-known case of Gary Dockery,
the brain-injured police officer who "woke up" and
interacted with his family for nearly twenty-four hours
30 after seven years of minimal responsiveness -- Chicago
Tribune 1/29/97 "After miracle coma patient has way to
go").

35 At present, however, there is a striking lack
of therapeutic options for these patients, despite
evidence of their capacity to further optimize their
brain function; this capacity is evident in the

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spontaneous fluctuations of functional level in many patients and the induced functional changes in some patients following sensory stimulation or patient initiated behaviors. The significance of developing a therapeutic intervention for patients having impaired cognitive function, especially those who remain conscious with preserved capacity for memory, attention, intention, and awareness lies in both the devastating reduction in quality of life they suffer and the economic burden these patients place on the health care system. These costs include full-time care in nursing and chronic rehabilitation facilities. Moreover, head trauma accounts for the largest percentage of these patients and most patients having impaired function caused by head trauma are under 40 years of age. These patients represent a disproportionate economic cost in terms of both the loss of their expected productivity and the attendant costs of very long-term full-time care based on their young age.

Thus, a need exists for methods for treating patients suffering from impaired cognitive function. The present invention is directed toward meeting this need.

SUMMARY OF THE INVENTION

The present invention relates to a method for treating a conscious patient having impaired cognitive function. The method includes selecting a conscious patient having impaired cognitive function. Electrical stimulation is then applied to at least a portion of the patient's intralaminar nuclei under conditions effective to relieve the patient's impaired cognitive function.

The present invention also relates to a method for improving coordination of function across cortical regions in a patient. The method includes applying electrical stimulation to two or more subdivisions of the

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patient's intralaminar nuclei. The two or more subdivisions of the patient's intralaminar nuclei modulate separate cortical regions.

Using the methods of the present invention, patients suffering from impaired cognitive function can have at least a portion of the function restored, thus improving their quality of life and reducing societal costs.

10 BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic diagram of the anatomical connections of the intralaminar nuclei with distributed circuits underlying arousal, attention, and gaze control.

Figures 2A-2E are photographs of brain sections illustrating intralaminar nuclei subdivisions suitable for stimulation in accordance with the practice of the present invention.

20 DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a method for treating a conscious patient having impaired cognitive function. The method includes selecting a conscious patient having impaired cognitive function. Electrical stimulation is then applied to at least a portion of the patient's intralaminar nuclei under conditions effective to relieve the patient's impaired cognitive function.

As used herein, cognitive function means the information processing capacities of the brain, including all semantic information processing, including interpretation of external and internal sensory signals and integration of those signals to support behavior. Perceptual awareness, as used herein, is a subset of cognitive function and is meant to include the mechanisms

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of selecting, organizing, and classifying internally or externally generated brain signals. A variety of methods can be used to assess a patient's cognitive function and to detect deficits in perceptual awareness. These
5 include clinical neurological and neuropsychological evaluation and administration of detailed neuropsychological test batteries.

The patient with impaired cognitive function may have that condition alone, or, alternatively, the
10 patient may suffer from a variety of other ailments in addition to impaired cognitive function. Such other ailments may include chronic pain or generalized seizures, each of which conditions may be present without the other. Alternatively, patients with impaired
15 cognitive function may additionally suffer from both chronic pain and generalized seizures. Patients with impaired cognitive function alone, patients with impaired cognitive function accompanied by either chronic pain or generalized seizures, and patients with impaired
20 cognitive function accompanied by both chronic pain and generalized seizures can all benefit from the practice of the present invention. As used herein, chronic pain means a syndrome of protracted pain, typically resulting from a persistent activation of central pain mechanisms
25 (i.e., in the brain (commonly referred to as "neuropathic pain") as opposed to pain which results primarily from activation of pain mechanisms in the peripheral nervous system. As used herein, generalized seizures is meant to include epileptic seizures, such as those experienced by
30 severe medication resistant refractory epileptics (i.e., patients who have been treated with multiple anti-epileptic medications at near toxic doses and failed this therapy as evidenced by their continuing to have multiple seizures daily despite such medication).

35 The method of the present invention can be practiced on patients whose cognitive dysfunction (e.g.,

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impaired perceptual awareness) is, for example, produced, at least in part, by brain injuries, including those produced, at least in part, by stroke, head trauma (e.g., blunt head trauma or missile penetration), toxicological agents (e.g., carbon monoxide, arsenic, or thallium), anoxia (e.g., reduced oxygen levels in the blood), ischemia (e.g., reduced blood flow), nutritional deficiencies, developmental diseases, infectious diseases, neoplastic diseases, degenerative diseases, complications thereof, or other structural lesions.

These brain injuries frequently manifest themselves in combined deficits of attention, intention, working memory, and/or awareness. As used herein, attention refers to the cognitive function that provides the capacities for selection of internal or external stimuli and thoughts, supports the preparation of intended behaviors (e.g., speeds perceptual judgements and reaction times), and supports the maintenance of sustained cognition or motor behaviors (e.g., the focusing of attention). Intention, as used herein, refers to the mechanism of response failures (i.e., lack of behavioral interaction) which is not due to a perceptual loss (i.e., intention is the cognitive drive linking sensory-motor integration to behavior). Intention deficits include failure to move a body part despite intact motor pathways, awareness, and sensory processing as demonstrated by neurophysiological and neuropsychological evaluation. Another example of a patient's intention deficit is a failure to initiate action of any kind despite evidence of awareness or action produced by stimulation. Loss of intention is a disorder of cognitive function, as defined herein, and is a major division of the neuropsychological disorder of neglect, which may be present in many patients with cognitive loss following brain injury. Working memory, as used herein, refers to the fast memory process

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required for on-line storage and retrieval of information, including processes of holding incoming information in short-term memory before it can be converted into long-term memory and processes which support the retrieval of established long-term (episodic) memories. Deficits in awareness relate to impaired perceptual awareness, as described above. Clinical signs of these brain injuries also include profound hemi-spatial neglect, disorders of motor intention, disorders of impaired awareness of behavioral control, or apathy and cognitive slowing.

A patient's attention, intention, working memory, and/or awareness function can be evaluated using standard tests. Most of these test batteries encompass the different types of basic cognitive functions and are used to initially screen a patient for a pattern of deficits. More specific tests can be employed and individualized to a patient's neuropsychological profile. In practice, the choice of particular neuropsychological test batteries depends on the experience of the tester and the normative data available for the test. This changes as new studies are done and as new testing materials are tried out and compared. For example, suitable comprehensive tests include the Mental Status Exam ("MSE") (set forth, for example, in Strub et al., The Mental Status Exam in Neurology, 3rd ed., Philadelphia:Davis (1993), which is hereby incorporated by reference) as well as broad neuropsychological test batteries, like the Halstead-Reitan Neuropsychological Test Battery (which encompasses memory, attention, intention, and perception/awareness). In order to delineate more narrowly specific deficits of working memory, attention, perception, etc., more individualized tests can be chosen. For example, a 'Shipley-Hartford scale' test may be employed to assess cognitive slowing (intelligence); a 'Bender-Gestalt' test can be used to

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assess spatial relations and constructions; Aphasia screening tests, such as the Boston Diagnostic Aphasia Examination or the Western Aphasia Battery, can detect language dysfunction; and Trials A/B or Memory Assessment Scales ("MAS") test can be used to assess working memory. Further details with regard to these and other tests for assessing a patient's attention, intention, working memory, and/or awareness function can be found in, for example, Berg, "Screening Tests in Clinical Neuropsychology," Chapter 10, pp. 331-363, in Horton et al., eds., The Neuropsychology Handbook, Vol. 1, Foundations and Assessment, 2nd ed., New York:Springer Publishing Company (1997), which is hereby incorporated by reference.

Clinical guidelines for patient selection are based on the patient's functional disturbance. For example, the patient's cognitive impairment may be slowing (or, in a severe case, dementia), as manifested in the patient's decreased attention, impaired intention, and decreased working memory. Alternatively, the patient may exhibit primary failure to initiate action despite interaction when stimulated. Patient selection in the clinical setting would also depend, in part, on prognostic signs, such as the presence of spontaneous fluctuations in functional level, modulation of functional level by external stimulation, or reliably produced modulation by internally generated stimulation.

As indicated above, the present invention relates to a method of treating a conscious patient having impaired cognitive function. Conscious, as used herein, has the conventional meaning, as set forth in Plum, et al., The Diagnosis of Stupor and Coma, CNS Series, Philadelphia:Davis (1982), which is hereby incorporated by reference. Conscious patients include those who have a capacity for reliable, reproducible, interactive behavior evidencing awareness of self or the

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environment. Conscious patients include patients who recover consciousness with less severe brain injury but who, because of their impaired cognitive function, do not reach independent living and remain in nursing facilities. Conscious patients do not include those who exhibit wakefulness but lack interaction (e.g., those deemed to be in a persistent vegetative state) A significant percentage, roughly 20% of patients who suffer severe brain damage remain conscious with preserved capacity for memory, attention, intention, and awareness. This is in contrast to patients who suffer from states of global unconsciousness, as indicated by conditions such as coma, persistent vegetative states, apallic state, coma vigil, and severe dementia.

Since adult patients in their twenties to forties have the most to gain from treatment and represent the greatest cost to society if left untreated, they would be preferred candidates for the intervention of the present invention. However, patients younger or older than those in the above age range would also benefit from the practice of the present invention. Although, in the early stages of clinical application, the method of the present invention will likely target more seriously compromised patients, it is believed that, ultimately, the method will have wider application to patients with mild to moderate cognitive impairment following brain injury as well. Patients suffering from post encephalitic parkinsonism or other disease processes which include oculogyric crises as a symptom are envisioned as being one class of patients who can be treated using the method of the present invention.

Once the conscious patient having impaired cognitive function is selected, electrical stimulation is applied to at least a portion of the patient's intralaminar nuclei under conditions effective to relieve the patient's impaired cognitive function.

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Generally, stimulation of the patient's intralaminar nuclei involves contacting the intralaminar nuclei with an electrode capable of delivering an electrical signal to the patient's intralaminar nuclei.

5 A variety of electrodes can be employed for delivering the stimulation. For example, suitable electrodes include the deep brain stimulation electrodes used in Katayama, "Characterization and Modification of Brain Activity with Deep Brain Stimulation in Patients in a

10 Persistent Vegetative State: Pain-Related Late Positive Component of Cerebral Evoked Potential," Pace, 14:116-121 (1991), which is hereby incorporated by reference, and the Medtronic DBS 3280 (available from Medtronic, Minneapolis, Minnesota), which has a flexible TEFLON-

15 SILASTIC™ coated, platinum iridium electrodes with 4 contacts, 4 mm tips, 2mm, mean tip separation, and an impedance of 5-7 kΩ within the brain, described in Velasco et al., "Electrocortical and Behavioral Responses Produced By Acute Electrical Stimulation of the Human

20 Centromedian Thalamic Nucleus," Electroencephalography and Clinical Neurophysiology, 102:461-471 (1997) ("Velasco"), which is hereby incorporated by reference. Preferably the electrode is an implantable multipolar electrode with either an implantable pulse generator that

25 can be under patient control or a radiofrequency controlled device operated by an external transmitter. Preferably, the multipolar electrode contacts should allow for adjustment of frequency (or "rate"), amplitude, and pulse width within at least the following respective

30 ranges: about 2-200 Hz, about 0.1-10 Volts, and about 50-500 microseconds. More preferably, the multipolar electrode contacts allow for adjustment in a broader range than those recited above, particularly toward higher intensities. Such preferred electrodes include a

35 Medtronic 3387 electrode (available from Medtronic, Minneapolis, Minnesota) and are described, for example,

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in Benabid et al., "Chronic Electrical Stimulation of the Ventralis Intermedius Nucleus of the Thalamus As a Treatment of Movement Disorders," J. Neurosurgery, 84:203-214 (1996), which is hereby incorporated by
5 reference. In some situations, it may be desirable to use an electrode capable of delivering pharmacological agents to the patient's intralaminar nuclei. Such electrodes include electrodes with microcannulae and are described in, for example, Hikosaka et al., "Modification
10 of Saccadic Eye Movements by GABA-related Substances. I. Effect of Muscimol and Bicuculline in Monkey Superior Colliculus. J. Neurophysiology, 53:266-291 (1985), which is hereby incorporated by reference. Examples of suitable pharmaceutical agents which can be used in
15 conjunction with the electrical stimulation methods of the present invention include known excitatory and inhibitory transmitters that influence intralaminar nuclei function. Excitatory transmitters would preferably include acetylcholine ("Ach"), noradrenaline
20 ("NE"), and/or serotonin ("5-HT") or analogues thereof. Inhibitory transmitters would include primary gamma-aminobutyric acid ("GABA") or analogs thereof. Other amino acid transmitters known to affect the intralaminar nuclei, such as adenosine or glutamate, can also be used.

25 The electrode can be contacted with the patient's intralaminar nuclei by the methods conventionally employed for embedding or emplacing electrodes for deep brain electrical stimulation in other thalamic nuclei. Such methods are described in Tasker et
30 al., "The Role of the Thalamus in Functional Neurosurgery," Neurosurgery Clinics of North America, 6(1):73-104 (1995) ("Tasker"), which is hereby incorporated by reference. Briefly, the multi-polar electrode or electrodes are introduced via burr holes in
35 the skull. The burr holes are placed based on the particular region of the intralaminar nuclei to be

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contacted. Preferably, prior to the introduction of the implantable multi-polar electrode(s), a detailed mapping with microelectrode and microstimulation following standard methods is carried out as described in Tasker, which is hereby incorporated by reference. Briefly, for each subdivision of the intralaminar nuclei, a preferred trajectory of approach optimizing the safety of entry point and maximal number of identifiable physiological landmarks in the responses of cell groups encountered along the trajectory into the desired region or regions of the intralaminar nuclei can be identified by one skilled in the art. This can be done, for example, by following the methods and catalogued physiological responses of different human thalamic cell groups described in Tasker, which is hereby incorporated by reference. Initial mapping of the path for the stimulating electrode(s) can, therefore, be carried out via a combination of detailed single-unit recording of receptive field ("RF") properties of the cells encountered along the trajectory, projective fields ("PF") mapped by microstimulation of the same cell groups, and comparison with known RF and PF responses in the human thalamus. Similarly, evoked potentials can be recorded and, for the intralaminar nuclei, have several characteristic signatures identifiable from scalp surface recording as discussed in Velasco and Tasker, which are hereby incorporated by reference. For this mapping, microstimulation, using tungsten microelectrodes with impedances of roughly 1.5 megaohms, every 1 mm at threshold of up to 100 microamperes with short trains of 300Hz pulses of 0.2 millisecond pulse width are employed as described in Tasker, which is hereby incorporated by reference. Typically, an on-line data base of RF and PF information along the trajectory and stereotactic coordinates derived, for example, from Schaltenbrand et al., Introduction to Stereotaxis with an Atlas of the

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Human Brain, Stuttgart:Thieme (1977), which is hereby incorporated by reference, or by computed mapping techniques, such as those described in Tasker et al., "Computer Mapping of Brainstem Sensory Centres in Man," J. Neurosurg., 44:458-464 (1976), which is hereby incorporated by reference, can be used, either with or without a magnetic resonance imaging ("MRI") based stereotactic apparatus. To carry out the above methods a patient would typically remain conscious with application of local anesthesia or mild sedation. However, in cases where a patient is not sufficiently cooperative to remain conscious during the procedure, the above-described approach can be modified to allow the operation to be completed under general anesthesia.

The electrical stimulation can be continuous, intermittent, or periodic. The range of stimulation frequencies and intensity of stimulation will depend on several factors: impedance of the electrode once in the brain, excitation properties of cells which may differ within subdivisions of the intralaminar nuclei, the type of induced physiologic responses sought for a particular patient, and interindividual variation. While higher frequency ranges are thought to be preferred, lower frequencies will also be employed. Suitable stimulation frequencies range from about 1 Hz to 1 kHz; preferably, from about 10 Hz to about 500 Hz; and, more preferably, from about 50 Hz to about 250 Hz.

Typically, the electrode is connected to an insulated conductor which leads to an external connector plug which is removably connected to a mating plug which is, in turn, connected to a voltage control and pulse generator. The pulse generator produces a selected pulse train, and the voltage control provides a selected current amplitude or voltage to the waves of the pulse train. Preferably, both the voltage control and pulse generator are under control of a computer microprocessor.

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The signal pulse generator should preferably be capable of generating voltage wave trains of any desired form (sine, square wave, spike, rectangular, triangular, ramp, etc.) in a selectable voltage amplitude in the range from about 0.1 volts to about 10 volts and at selectable frequencies as set forth above. In practice, the pulse train and voltage amplitudes employed will be selected on a trial and error basis by evaluating a patient's response to various types and amplitudes of electrical stimulation over a time course of from about 1 to about 12 months. For example, after implanting the electrode in the patient's intralaminar nuclei, stimulation with a voltage within the range of from about 0.1 to about 10 volts or higher, a rate within the range of from about 50 to about 250 Hz, and a pulse width within the range of from about 50 to about 500 microseconds is applied for from about 8 to about 12 hours a day. During and after the implantation of the electrode, the parameters of the stimulation (voltage, pulse width, and frequency) are adjusted to optimize the patient's interactive behavior. The stimulation parameters can be further optimized by monitoring the patient clinically, anatomically, physiologically, or metabolically to assess his or her response to the stimulation. For example, the patient can be physiologically examined using electroencephalogram ("EEG"), magnetoencephalogram ("MEG"), or functional magnetic resonance imaging ("fMRI"). Metabolic evaluation can be carried out, for example, using quantitative fluorodeoxy-glucose positron emission tomography ("FDG-PET"). In addition, correlation of induced changes in surface electrical brain activity (as measured, for example, by EEG or MEG) can be correlated with improved function and increased resting metabolism of a damaged brain regions as identified by FDG-PET. Careful evaluation of these different indices of brain function in conjunction with

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standard neurological and neuropsychological tests can thus be used to optimize the beneficial effect of the stimulation method of the present invention.

Intralaminar nuclei are a small set of nuclei located in the paramedian thalamus. The intralaminar nuclei can be divided into an anterior group and a posterior group. Figure 1 illustrates the anatomical connections of the intralaminar nuclei with distributed circuits underlying arousal, attention, intention, working memory, and gaze and motor control. The anterior group projects widely throughout the neocortex to primary sensory and motor areas and association cortices, while the posterior group projects mainly to sensory-motor and premotor areas and striatal targets. The anterior IL group includes the central lateral nucleus ("CL"), which projects to the frontal eye field ("FEF"), motor cortex, and, more heavily, to the posterior parietal cortex ("PPC"). The paracentralis ("Pc") nucleus projects to the prefrontal cortex (with heavier projection than CL) and very strongly to the inferior parietal lobe and visual association cortices. The central medial ("CeM") nucleus, which also projects to the prefrontal and visual association cortices, also projects to the cingulate cortex and pregenual areas and to the medial cortical surface and orbitofrontal cortex. Included within the meaning of intralaminar nuclei, as used herein, is the Paraventricular nucleus ("Pv"), which is strongly associated with the limbic system, and midline thalamic nuclei. Projections to prefrontal cortex ("PFC") and anterior cingulate cortex arise, as well, from the anterior intralaminar group. The CL is also known to project to the primary visual cortex in the cat and monkey. The posterior group is dominated by the centromedian-parafascicularis complex ("Cm-Pf"), which strongly projects to areas 6 and 4. In primates, the Cm-Pf undergoes a notable expansion, and the CL also expands

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and develops further subdivisions. This system projects strongly to the caudate (from Pf), putamen (from Cm nuclei of the basal ganglia), and prefrontal and parietal association cortices. A small projection (Pf) also goes
5 to the FEF. The intralaminar nuclei projections to the striatum per se are considered the principle efferent connections of the intralaminar nuclei and include anterior group projections to the caudate, as well. Thus the intralaminar nuclei (including the midline nuclei)
10 are believed to be in a preferred position to modulate the large thalamo-cortical-basal ganglia loops, especially to synchronize their function (Groenewegen et al., "The Specificity of the 'Nonspecific' Midline and Intralaminar Thalamic Nuclei," Trends in Neuroscience
15 17:52-66 (1994), which is hereby incorporated by reference.

The intralaminar nuclei receive ascending inputs from several components of the ascending reticular arousal system, including the pedunculopontine
20 cholinergic group (lateral dorsal tegmentum), mesencephalic reticular formation, locus ceruleus, and dorsal raphe. Thus, the intralaminar nuclei are targets of modulation by a wide variety of neurotransmitter agents, including acetylcholine (pedunculopontine,
25 lateral dorsal tegmentum, and mesencephalic reticular formation neurons), noradrenaline (locus ceruleus) serotonin (raphe nuclei), and histamine (hypothalamus). Also received by the intralaminar nuclei are nociceptive, cerebellar, tectal, pretectal, and rhinencephalic inputs.
30 Descending inputs reciprocally relate components of the intralaminar nuclei with their cortical projections.

Although each cell group within the intralaminar nuclei projects to many separate cortical targets, each neuron of the intralaminar nuclei has a
35 narrowly elaborated projection and receives its cortical feedback from the same restricted area. The reciprocal

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projections between the intralaminar nuclei and cortex have a distinctive laminar pattern that differs from the more well-known pattern of the reciprocal projections of the relay nuclei. The intralaminar nuclei neurons
5 synapse in Layer I on the terminal dendritic tufts of layers III and V pyramidal cells and in layers V and VI, whereas neurons of the relay nuclei terminate primarily in cortical layers III and IV. Feedback to intralaminar nuclei neurons originates in Layer V, but feedback to the
10 relay nuclei originates in Layer VI. In the cat, the dominant corticothalamic input to the CL originates in the PFC, whereas the visual areas, including area 17, also project directly to the CL.

As used herein, intralaminar nuclei also
15 include paralamellar regions, such as parts of the medial dorsal ("MD") nucleus and the midline nuclei (which are sometimes distinguished from the intralaminar nuclei but, for purposes of the present application, are not).

Figures 2A-2E illustrate intralaminar nuclei
20 subdivisions suitable for stimulation in accordance with the practice of the present invention. Table 1 sets forth the meanings of the abbreviations used in Figures 2A-2E (See Buren et al., Variations and Connections of the Human Thalamus, New York: Springer-Verlag (1972),
25 which is hereby incorporated by reference).

Table 1

| Term | | Sagittal | Horizontal | Transverse |
|-------------------|---|------------------------------|------------------|--|
| A | — N. amygdalae | S — L 12.0-22.0 | | T — A 20.3 (PC)-10.9 (PC) |
| Ad | — N. anterodorsalis | S — L 3.0 | H — S 13.2 | T — A 20.3 (PC)-14.1 (PC) |
| A pr | — N. anteroprecipalis | S — L 3.0-9.0 | H — S 13.2-6.3 | T — A 23.4 (PC)-10.9 (PC), 4.7 (PC) |
| B | — N. basalis | S — L 6.0-22.0 | H — 14.5-8.1 | T — A 23.4 (PC)-10.9 (PC) |
| B cj | — Brachium conjunctivum | | H — 18.1 | |
| B co i | — Brachium colliculi inferioris | S — L 9.0 | H — 14.5 | T — P 1.6 (PC), 4.7 (PC) |
| B co s | — Brachium colliculi superioris | S — L 9.0 | H — 14.5 | |
| C cl s | — Corporis callosi splenium | S — L 2.0-3.0 | | |
| Cd | — N. caudatus | S — L 6.0, 12.0-25.0 | H — S 17.0-13.2 | T — A 23.4 (PC)-P 4.7 (PC) |
| Ce mc | — N. centralis magnocellularis | S — L 9.0 | H — S 2.7 | T — A 7.8 (PC)-1.6 (PC) |
| Ce pc | — N. centralis parvocellularis | S — L 9.0-12.0 | H — S 6.3-10.9 | T — A 7.8 (PC)-1.6 (PC) |
| Cl | — Claustrum | | H — S 17.0, 9.7 | T — A 23.4 (PC) |
| Cm | — Corpus mammillare | S — L 2.0, 2.5 | | T — 14.1 (PC) |
| Cm a | — Commissura anterior | S — L 2.0, 6.0, 12.0-25.0 | H — S 2.7, 18.1 | T — A 23.4 (PC)-17.2 (PC) |
| Cm p | — Commissura posterior | S — L 2.0, 3.0 | H — S 2.7, 10.9 | T — P 1.6 (PC) |
| Cn A | — Cornu Ammonis | S — L 19.0-25.0 | H — 10.9, 18.1 | T — A 7.8 (PC)-1.6 (PC) |
| Co | — N. commissuralis | S — L 2.0-2.5 | H — S 2.7 | T — A 20.3 (PC)-10.9 (PC) |
| Co s | — Colliculus superior | S — L 2.0-6.0 | H — 10.9, 4.5 | T — P 4.7 (PC) |
| D c | — N. dorsocaudalis | S — L 12.0-19.0 | H — S 13.2, 9.7 | T — A 7.8 (PC)-1.6 (PC) |
| D o | — N. dorsooralis | S — L 9.0-19.0 | H — S 17.0-9.7 | T — A 17.2 (PC)-7.8 (PC) |
| D sf | — N. dorsalis superficialis | S — L 6.0-12.0 | H — S 17.0, 13.2 | T — A 10.9 (PC)-4.7 (PC) |
| Edy | — N. edymalis | S — L 2.0, 2.5 | H — 10.9 | T — A 17.2 (PC)-10.9 (PC), 4.7 (PC) |
| F | — Fornix | S — L 2.0-3.0 | H — S 17.0-18.1 | T — A 23.4 (PC)-14.1 (PC), P 1.6 (PC), 4.7 (PC) |
| Fa | — N. fasciculosus | S — L 3.0, 6.0 | H — S 2.7-10.9 | T — A 23.4 (PC)-17.2 (PC) |
| G l mc | — Corpus geniculatum laterale, magnocellularis | S — L 19.0-25.0 | H — 14.5, 8.1 | T — A 1.6 (PC), P 1.6 (PC) |
| G l pc | — Corpus geniculatum laterale, parvocellularis | S — L 19.0-25.0 | H — 14.5, 8.1 | T — A 1.6 (PC), P 1.6 (PC) |
| G m mc | — Corpus geniculatum mediale, magnocellularis | S — L 12.0 | H — 14.5 | T — P 1.6 (PC) |
| G m pc | — Corpus geniculatum mediale, parvocellularis | S — L 12.0, 16.0 | H — 10.9, 4.5 | T — A 1.6 (PC), P 1.6 (PC) |
| Gr ce me | — Grisea centralis mesencephali | S — L 2.0-3.0 | H — 14.5, 8.1 | T — P 1.6 (PC), 4.7 (PC) |
| cf H ₁ | — Campus Forelii H ₁ | S — L 6.0, 9.0 | H — 14.5 | T — A 10.9 (PC) |
| cf H ₂ | — Campus Forelii H ₂ | S — L 6.0, 9.0 | H — 14.5 | T — A 10.9 (PC) |
| H l | — N. habenularis lateralis | S — L 3.0 | H — S 6.3, 2.7 | T — A 1.6 (PC) |
| H m | — N. habenularis medialis | S — L 2.0-3.0 | H — S 6.3, 2.7 | T — A 1.6 (PC) |
| Hpth | — Hypothalamus | S — L 2.0-6.0 | H — 10.9-8.1 | T — A 23.4 (PC)-10.9 (PC) |
| iLa | — N. intralamellaris | S — L 2.0-12.0 | H — S 13.2-2.7 | T — A 17.2 (PC)-1.6 (PC) |
| I s | — N. interstitialis (Cajal) | | | T — A 1.6 (PC), P 4.7 (PC) |
| Li | — N. limitans | S — L 6.0-12.0 | H — 10.9 | T — P 1.6 (PC) |

Table 1 (continued)

| Term | Sagittal | Horizontal | Transverse |
|--|------------------------|------------------|---|
| L l — Lemniscus lateralis | | | T — P 1.6 (PC), 4.7 (PC) |
| L m — Lemniscus medialis | | H — I 4.5, 8.1 | |
| L po — N. lateropolaris | S — L 6.0-16.0 | H — S 13.2-I 0.9 | T — A 23.4 (PC)-14.1 (PC) |
| M — N. medialis | S — L 2.0-9.0 | H — S 13.2-2.7 | T — A 17.2 (PC)-1.6 (PC) |
| N III — N. oculomotorius | S — L 2.0 | | T — A 1.6 (PC)-P 4.7 (PC) |
| N V me — N. nervi trigemini mesencephalicus | | | T — P 4.7 (PC) |
| N EW — N. Edinger Westphal | S — L 2.0 | | T — A 4.7 (PC)-P 4.7 (PC) |
| Pf — N. parafascicularis | S — L 6.0 | H — I 0.9 | T — A 7.8 (PC)-1.6 (PC) |
| Pi — Pincal | S — L 2.0-3.0 | | T — P 4.7 (PC) |
| Pl — Pallidum laterale | S — L 9.0-22.0 | H — S 6.3-I 4.5 | T — A 23.4 (PC)-7.8 (PC) |
| P m — Pallidum mediale | S — L 9.0-19.0 | H — S 2.7-I 4.5 | T — A 23.4 (PC)-10.9 (PC) |
| P m a — N. paramedianus anterior | S — L 2.0-2.5 | H — S 2.7 | T — A 20.3 (PC)-10.9 (PC) |
| P m p — N. paramedianus posterior | S — L 2.0-2.5 | H — S 2.7 | T — A 7.8 (PC)-1.6 (PC) |
| P pd — N. peripeduncularis | S — L 12.0 | H — I 4.5, 8.1 | T — A 1.6 (PC) |
| Pret — Area preectalis | S — L 6.0 | H — I 0.9, 4.5 | T — P 1.6 (PC) |
| Pr G — N. praegeniculatus | S — L 19.0-23.0 | H — I 4.5, 8.1 | T — A 1.6 (PC) |
| Pt — N. parataenialis | S — L 2.0-3.0 | H — S 9.7-2.7 | T — A 20.3 (PC)-7.8 (PC) |
| Pu i — N. pulvinaris intergeniculus | S — L 12.0 | H — I 4.5 | T — P 1.6 (PC) |
| Pu l — N. pulvinaris lateralis | S — L 16.0-22.0 | H — S 13.2-I 0.9 | T — A 1.6 (PC)-P 4.7 (PC) |
| Pu m — N. pulvinaris medialis | S — L 6.0-16.0 | H — S 13.2-I 0.9 | T — A 1.6 (PC)-P 4.7 (PC) |
| Pu o — N. pulvinaris oralis | S — L 12.0 | H — S 6.3, 2.7 | T — A 1.6 (PC) |
| Put — Putamen | S — L 19.0-25.0 | H — S 13.2-I 8.1 | T — A 23.4 (PC)-7.8 (PC) |
| Pv — N. paraventricularis hypothalami | S — L 2.5, 3.0 | H — I 0.9-8.1 | T — A 23.4 (PC), 20.3 (PC) |
| R — N. reticularis | S — L 6.0-25.0 | H — S 17.0-I 0.9 | T — A 23.4 (PC)-4.7 (PC), P 1.6 (PC), 4.7 (PC) |
| Ru — N. ruber | S — L 2.0-6.0 | H — I 4.5-8.1 | T — A 7.8 (PC)-1.6 (PC) |
| S m th — Stria medullaris thalami | S — L 2.0-3.0 | H — S 9.7, 6.3 | T — A 23.4 (PC)-1.6 (PC) |
| S n — Substantia nigra | S — L 6.0-12.0 | H — I 8.1 | T — A 14.1 (PC)-1.6 (PC) |
| So — N. supraopticus hypothalami | S — L 3.0-6.0, 12.0 | | T — A 23.4 (PC), 20.3 (PC) |
| Sth — N. subthalamicus | S — L 6.0-12.0 | H — I 4.5, 8.1 | T — A 14.1 (PC)-7.8 (PC) |
| TI — Nucleus tuberis lateralis | S — L 6.0 | | |
| T M — Tractus Mernerti | S — L 2.0-6.0 | H — S 2.7-I 8.1 | T — A 7.8 (PC)-1.6 (PC) |
| T m th — Tractus mammillothalamicus | S — L 2.5-6.0 | H — S 6.3-I 8.1 | T — A 17.2 (PC), 14.1 (PC) |
| TO — Tractus opticus | S — L 2.5-22.0 | | T — A 20.3 (PC)-4.7 (PC) |
| V ce — N. ventrocaudalis externus | S — L 16.0-19.0 | H — S 9.7-I 0.9 | T — A 7.8 (PC)-1.6 (PC) |
| V ci — N. ventrocaudalis internus | S — L 12.0-16.0 | H — S 6.3-I 0.9 | T — A 7.8 (PC)-1.6 (PC) |
| V c pc — N. ventrocaudalis parvocellularis | S — L 9.0-12.0 | H — I 0.9 | T — A 7.8 (PC), 4.7 (PC) |
| V c v — N. ventrocaudalis ventralis | S — L 16.0 | H — I 4.5 | T — A 7.8 (PC)-1.6 (PC)) |
| V im — N. ventrointermedius | S — L 9.0-19.0 | H — S 6.3-I 0.9 | T — A 10.9 (PC)-4.7 (PC) |
| V oe — N. ventrooralis externus | S — L 9.0-16.0 | H — S 13.2-I 0.9 | T — A 17.2 (PC)-7.8 (PC) |
| V oi — N. ventrooralis internus | S — L 6.0 | H — S 9.7-I 0.9 | T — A 14.1 (PC), 10.9 (PC) |
| Z i — Zona incerta | S — L 6.0-16.0 | H — I 4.5 | T — A 17.2 (PC)-4.7 (PC) |

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For example, the stimulated intralaminar nuclei subdivisions can include the centromedian-parafascicularis or the central lateral or both. Alternatively, the stimulated portion of the patient's intralaminar nuclei
5 can be selected so that it does not include the centromedian-parafascicularis, the central lateral, or either the centromedian-parafascicularis or the central lateral nuclei.

The electrical stimulation can be applied to
10 the patient's entire intralaminar nuclei or to one or more portions of the patient's intralaminar nuclei. In addition to being applied to the patient's intralaminar nuclei or portion thereof, the electrical stimulation can also extend to other regions of the brain. Preferably,
15 the electrical stimulation is applied only to the patient's intralaminar nuclei or portion thereof without stimulating other regions of the patient's brain. For example, the electrical stimulation can be applied to all portions of the patient's intralaminar nuclei except the
20 centromedian-parafascicularis, except the central lateral, or except both the central lateral and centromedian-parafascicularis.

The method of the present invention can further comprise selecting one or more subdivisions of the
25 patient's intralaminar nuclei for stimulation. In particular, the subdivision to be stimulated can be one which modulates the specific cognitive function which is impaired in the patient. For example, Table 2 sets forth various subdivisions of the intralaminar nuclei and the
30 specific cognitive function with which each is associated.

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Table 2

| Specific ILN Subdivision | Cognitive Function Impairment |
|-------------------------------|---|
| centromedian-parafascicularis | attention deficits, anosognosia, working memory deficits, intentional deficits, nonsensory neglect, akinesia, frontal lobe damage |
| 5 central lateral | perceptual impairment, sensory neglect, visuomotor impairment, working memory deficits, attentional deficits, anosognosia |
| paracentralis | working memory deficits, apathy, emotional dyscontrol |
| paraventricularis | loss of awareness of emotional/limbic signals |
| central medial | apathy, emotional dyscontrol, intentional deficits |

10

Further details regarding the identification of intralaminar nuclei subdivisions which modulate specific cognitive function can be found in, for example, Macchi et al., "The Thalamic Intralaminar Nuclei and the Cerebral Cortex," pp. 355-389, in Jones et al., eds., Cerebral Cortex, Vol. 5, New York:Plenum Press (1986), Castaigne et al., "Paramedian Thalamic and Midbrain Infarcts: Clinical and Neuropathological Study," Ann. Neurol., 10:127-148 (1980), and Purpura et al., "The Thalamic Intralaminar Nuclei: A Role in Visual Awareness," The Neuroscientist, 3:8-15 (1997) ("Purpura"), which are hereby incorporated by reference. Thus, by knowing the specific cognitive function or functions impaired in a particular patient, the preferred

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subdivision of the particular patient's intralaminar nuclei to receive electrical stimulation can be determined.

5 In cases where the patient suffers from post-encephalitic parkinsonism or other disease processes which include oculogyric crises as a symptom, it is believed that the preferred intralaminar nuclei subdivision is the central medial.

10 Once the particular subdivision to be stimulated is selected, that subdivision and, optionally, others are stimulated as described above. That is, electrical stimulation can be applied to the selected subdivision only, or, alternatively, electrical stimulation can be applied to the selected subdivision as
15 well as other subdivisions of the patient's intralaminar nuclei. Stimulation can be applied to the selected subdivision and optional other subdivisions of the intralaminar nuclei in either or both brain hemispheres.

20 Preferably, the intralaminar nuclei subdivision which is to receive electrical stimulation is one which projects to an area of the brain which has reduced baseline function but which also exhibits increased function during periods of external stimulation or internally generated stimulation, such as patient's self-
25 generated activity (e.g., head turning).

In many cases, patients with cognitive impairments following brain injury can have their cognitive function modulated by various forms of external stimulation. For example, in some patients, stimulation
30 of the brainstem vestibular system with cold water caloric stimulation of the external ear canal, such as described in Gainotti, "The Role of Spontaneous Eye Movements in Orienting Attention and in Unilateral Neglect," pp. 107-113, in Robertson et al., eds.,
35 Unilateral Neglect: Clinical and Experimental Studies, Hove, United Kingdom:Lawrence Erlbaum Associates,

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Publishers (1993) and Vallar et al., "Modulation of the Neglect Syndrome by Sensory Stimulation," pp. 555-578, in Thier et al., eds., Parietal Lobe Contributions to Orientation in 3D Space, Heidelberg, Germany:Springer-Verlag (1997), which are hereby incorporated by reference, generates transient but profound recovery of multiple cognitive functions including self-awareness, intention, and perceptual awareness. Other external stimulation that may modulate cognitive function, would include alteration of trunk, head, or limb position signals, such as a vibrational stimulation of the sternocleidomastoid muscle.

Similarly, some patients with less severe global impairments of consciousness discover strategies to self-generate behaviors that assist in supporting their cognitive or perceptual function. For example, some patients with visual agnosias who have visual perceptual problems discover that self-generated rhythmic head movements or hand tracing movements improve their visual awareness and cognitive skills in identifying figures. These self-generated rhythmic head and hand movements are described in Farah, Visual Agnosia, Cambridge, Massachusetts:MIT Press (1990), which is hereby incorporated by reference.

It is believed that the capacity to modulate cognitive function by external or internal stimulation in these patients demonstrates that certain brain activations can optimize their function. In the case of vestibular stimulation, it is believed that the intralaminar nuclei are directly implicated by their strong inputs from the vestibular nuclei. Although the present invention is not intended to be limited by the mechanism by which it operates, it is believed that the intralaminar nuclei's role in supporting these function relates to the generation of event-holding functions that may promote interaction across the cortex, possibly by

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enhancing synchronization, as described in Purpura. One theory of the present invention is that similar event-holding functions tied to head, hand, trunk or other bodily coordinates are generated by intralaminar nuclei stimulation and account for the improved cognitive function seen in patients who are externally or internally stimulated. Whether or not such other modulations are directly tied to intralaminar nuclei stimulation, functional studies in an individual patient, such as those carried out in Bottini et al, "Modulation of Conscious Experience by Peripheral Sensory Stimuli," Nature, 376:778-781 (1995), which is hereby incorporated by reference, can be used to identify specific cortical regions that are modulated as an initial step in applying the method of the present invention.

Although the above described method for selecting a subdivision of the patient's intralaminar nuclei to which to apply electrical stimulation in accordance with the present invention is acceptable, in many cases, it is preferred to determine, on an individual basis, which areas of the brain have reduced baseline function, and then to correlate the area of the brain having reduced baseline function with an intralaminar nuclei subdivision which projects thereto. As one skilled in the art would recognize, determining areas of the brain which have reduced baseline function can be carried out advantageously using quantitative metabolic information obtained from a FDG-PET study of resting brain metabolism; using electromagnetic indicators of regional functional activity; anatomically, physiologically, or metabolically; or using combinations of these methods. As used herein, baseline brain function is defined within the patient and across a database of normal values for resting cerebral metabolism and is typically measured in terms of glucose uptake and utilization. One particularly useful gauge of baseline

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brain function is the regional cerebral metabolic rate as measured using fluorodeoxyglucose ("rCMRgluc"). This is quantitated by fluorodeoxyglucose-PET measurements and compared across brain structures within the patient's brain and against normative values for particular brain regions. Further details regarding assessing baseline brain function are described in, for example, Mazziota, ed., Clinical Brain Imaging, CNS Series, Philadelphia:Davis (1992), which is hereby incorporated by reference. Once the portion of the brain having reduced baseline function is identified, the portion can be correlated with the intralaminar nuclei ("ILN") subdivision which projects to this region, for example, by using Table 3.

Table 3

| Specific ILN Subdivision | Primary Cortical Targets |
|-------------------------------|---|
| centromedian-parafascicularis | prefrontal cortex, premotor cortex, parietal cortex |
| central lateral | prefrontal cortex, parietal cortex, visual association cortex, motor cortex |
| paracentralis | prefrontal cortex, orbitofrontal cortex |
| paraventricularis | amydala, limbic system |
| central medial | orbitofrontal cortex |
| paralam MD | prefrontal cortex |
| midline nuclei | hippocampus, limbic system |

Further details regarding the correlation of areas of the brain to the intralaminar nuclei subdivisions which project thereto can be found in, for example, Jones et

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al., eds., The Thalamus, Amsterdam:Elsevier (1995), which is hereby incorporated by reference. When a subdivision is selected in this manner, electrical stimulation can be applied to the selected subdivision only, or,
5 alternatively, it can be applied to the selected subdivision and, in addition, to other subdivisions of the patient's intralaminar nuclei.

As indicated above, electrical stimulation can be applied to the entire group of intralaminar nuclei or
10 to one, two, or more specific subdivisions thereof. Stimulation can be applied to the one, two, or more specific subdivisions in either or both brain hemispheres. In some cases, it can be advantageous to apply electrical stimulation to two or more subdivisions
15 of the intralaminar nuclei which modulate separate cortical regions. As used herein, cortical regions are considered to be separate when they are not contiguous on the cortical mantle or they are considered separate in function based on known anatomical or physiological
20 characteristics of cells within their borders. For example, the patient's central medial and centromedian-parafascicularis intralaminar nuclei subdivisions, which respectively project strongly to the orbitofrontal and premotor regions of the cortex, can be stimulated. Where
25 two or more subdivisions of the intralaminar nuclei are stimulated, both can lie in the same thalamus. Alternatively, at least one of the two or more subdivisions of the intralaminar nuclei can lie in the left thalamus while at least one of the two or more
30 subdivisions of the intralaminar nuclei lies in the right thalamus. Preferably, at least one of the two or more subdivisions and, more preferably, at least two of the two or more subdivisions of the intralaminar nuclei to which electrical stimulation is applied modulates the
35 specific cognitive function which is impaired in the patient.

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Where two or more subdivisions of the patient's intralaminar nuclei are electrically stimulated periodically and at the same frequency, such stimulation can be completely in phase, partially in phase and partially out of phase, or completely out of phase. When such stimulation is substantially entirely in phase, it is said to be synchronized. In a preferred embodiment of the present invention, the electrical stimulation applied to two or more subdivisions of the patient's intralaminar nuclei is synchronized. It is believed that activation of separate cortical regions by common intralaminar nuclei inputs promotes coordinated processing in these separated cortical regions because of the strong capacity of these intralaminar inputs to generate depolarization of neurons in the supragranular layers (upper) of the cerebral cortex. It is believed that such strong depolarization generates improved synchronization of neuronal activity across cortical regions. This improved synchronization may result from high frequency oscillations excited by these inputs or sustained enhancement of neural activity seen in the form of broadband activity or increased average power across a cortical region. More particularly, the method of the present invention can be optimized by monitoring regional and intrahemispheric changes in brain waves (e.g., changes in absolute power, relative power, and/or intra- and/or inter-regional coherence) as measured by using conventional techniques (e.g., EEG or MEG techniques) or by monitoring regional and intrahemispheric changes in metabolic activity. As indicated above, metabolic activity can be assessed using conventional methods (e.g., positron emission tomography ("PET") or FDG-PET).

The result of intralaminar nuclei stimulation under one aspect of the present invention is that correction of functional disconnections of brain regions by release of inhibition of remaining cortical or

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subcortical regions may be achieved by stimulation of the appropriately connected intralaminar nuclei; such release of inhibition may increase metabolic activity in suppressed areas. Alternatively, such stimulation may result in an alteration of population activity of many neurons in a local cortical area that improves information transfer or processing capacities of the neurons in that region (for example, by sharpening their receptive fields). Under another aspect of the present invention, synchronization of stimulated areas may facilitate a broader integration of cortical processing via synchronization of activity within the intralaminar nuclei of each thalamus and promote a global integrative process at the level of the cortex. Similarly, intralaminar nuclei connected to cortical areas known to be important for specific cognitive functions independent of a patient's particular injury, but selected by the patient's behaviorally evidenced impairment, may be selected for stimulation.

Selection of a particular strategy of intralaminar nuclei stimulation for a given patient will depend on several features including the specific cortical regions a given subdivision of the intralaminar nuclei projects to, particular stimulation parameters, evidence of modulation of cognitive function by external stimulation, internally generated stimulation (e.g., head turning), or spontaneously, and the patient's underlying brain damage and/or behavioral dysfunction. Optimization of the preferred method of the present invention involves promoting coordinated information processing or enhanced participation in integrated brain function of cortical regions innervated by intralaminar nuclei. If possible, this optimization can be based on evidence of improved function with reliable external (or internal) stimulation procedures or indexed by strong clinical inferences and

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functional anatomic information based on areas of identified hypometabolism or anatomical disconnection.

As one skilled in the art will recognize, optimization of the method of the present invention can
5 be achieved by varying specific stimulation parameters (such as intensity, frequency, pulse width, on time and off time, and duty cycle) while monitoring cognitive function as assessed by standard neuropsychologic instruments of working memory, attention, and/or
10 intention. Optimization can also be effected by monitoring specific regional and intrahemispheric changes in distribution of signal power and coherence within the frequency spectrum.

It is believed that the mechanism which permits
15 treatment of patients having impaired cognitive function with electrical stimulation of his or her intralaminar nuclei is based, in part, on applicant's newly theorized role for the intralaminar nuclei in cognitive operations, which is set forth in Purpura, which is hereby
20 incorporated by reference. Although the present invention is not meant in any way to be limited by the mechanism in which it operates, for example, as set forth in Purpura, it is believed that the proposed mechanism may assist in optimizing the method of the present
25 invention.

In another aspect of the present invention, coordination of function across cortical regions in a patient is improved by applying electrical stimulation to two or more subdivisions of the patient's intralaminar
30 nuclei. Improved coordination of function across cortical regions, as used herein, is meant to include improved functional interactions of specific cortical regions within and across left and right hemispheres, such as those discussed above in regard to the effects of
35 vestibular stimulation. In this method, the two or more subdivisions of the patient's intralaminar nuclei

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modulate separate cortical regions. Preferably, the electrical stimulation applied to the two or more subdivisions of the intralaminar nuclei is synchronized or periodic, more preferably, synchronized and periodic.

5 Suitable frequencies for use in the method of this aspect of the present invention range from about 1 Hz to 1 kHz; preferably, from about 10 Hz to about 500 Hz; and, more preferably, from about 50 Hz to about 250 Hz.

Several possible mechanisms may explain the improved coordination of function across cortical regions which is believed to result from application of electrical stimulation to two or more subdivisions of the patient's intralaminar nuclei. These include changes in global dynamics of a distributed neural network, changes

15 in inhibition or excitation at one or more points in large loops of circuits activated by ILN inputs, and increases in metabolic rates that change the firing rates or other cellular processes. Also, increases in synchrony may promote increased firing rate and increased

20 metabolism or vice versa.

Applicant's copending U.S. Provisional Patent Application Serial No. 60/062,728, filed October 22, 1997, is hereby incorporated by reference.

The present invention is further illustrated by

25 the following examples.

EXAMPLES

Example 1 -- Clinical History

30 A 28 year old man with no past medical history suffers coup and contre coup head injuries in a motor vehicle accident. MRI imaging reveals a large hemorrhage of the right parietal cortex, left prefrontal, and bilateral (left greater than right) orbitofrontal white

35 matter. These changes are consistent with contre coup injury. In addition, the patient has small petechial

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areas of blood in the corpus callosum consistent with shear force injury. The patient is comatose initially for 2 weeks and gradually recovers consciousness over a 4-8 week period, achieving a new baseline which stabilizes at 3 months. Over the next six months the patient is noted to demonstrate fluctuations of interactive behavior. At baseline, the patient neglects the left side of his body which typically exhibits no spontaneous movement. At other times the patient will spontaneously interact, speak and follow commands. He remains usually stimulus-bound (i.e., he is dependent on prompting by those around him and exhibits a paucity of spontaneous behavior). His "good" times last for weeks, as do his "bad" times where he is awake but minimally interactive. Although, at times, he is nearly able to feed himself and/or perform other basic activities of daily living, on average, his fluctuations and profound short-term memory impairments require that he remain in a full-time nursing facility despite his family's strong desire to care for him at home.

Example 2 -- Intervention

Because, at his best, the patient in Example 1 is close to a level where part-time care at home would be possible (e.g., within 10 points on a Karnofsky scale of function), he is evaluated for deep brain stimulation to optimize his brain function. In the course of evaluation, several important observations are made. First, the patient's left-sided neglect, attributable to the right parietal hemorrhage, is markedly improved upon irrigation of the left external ear canal. In addition, irrigation of the left external ear canal produces spontaneous movements of the left arm. Second, FDG-PET reveals depressed right parietal, left prefrontal, and left greater than right orbitofrontal metabolism compared against other regions within the patient's brain that are

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within normal ranges and against normative values for these brain areas. Third, there is MEG evidence of decreased high frequency activity over the right parietal cortex and left prefrontal cortex. This correlates with the FDG-PET evaluation. Based on these observations, the patient is chosen for the deep brain stimulation method of the present invention.

Using the clinical, MRI, PET, and MEG data, the following intralaminar nuclei subdivisions are chosen for stimulation. The rationale for choosing these sites is explained below. The patient's spontaneous fluctuations support the interference that several different dynamic patterns may organize this patient's brain function at any one time, with some patterns more optimal than others. The injuries to the right parietal cortex (the dominant cortical area for attention) and the left prefrontal and orbitofrontal (important for working memory, motor planning, and intention) suggest the cortical areas where intervention may push the brain toward the more optimal pattern. The presence of metabolic and physiologic activity depressed below normal levels indicates both that some function remains in these areas but that this function is abnormal. Intralaminar nuclei subdivisions are chosen to modulate these cortical areas.

The right centromedian-parafascicularis ("Cm-Pf") nucleus is chosen for several reasons, including its strong projections to the parietal and premotor cortices in the right hemisphere, which cortices modulate the motor neglect and attentional impairments evident in this patient. In addition, the evidence of shear injury on the MRI and history of coma suggest damage to ascending arousal inputs to the cortex which could be supported by increased activation of the Cm-Pf nucleus which is most strongly innervated by the arousal systems. Placement of such Cm-Pf electrodes is well-known in the art.

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The left paracentralis ("Pc"), central lateral ("CL"), and paralamellar MD regions of the intralaminar nuclei are also chose as targets. Since these are small and closely spaced, the multipolar electrode is likely to
5 activate at least one or two of these targets with each contact when optimally placed. Placement of this electrode is guided by the activation of widespread but specific cortical areas by stimulation of the lateral aspect of CL along its anterior-posterior extent (See,
10 for example, Tasker, which is hereby incorporated by reference). These areas are chosen because of their strong inputs to prefrontal cortex (Pc, paralamellar MD>CL) and, in the case of paralamellar MD, known influence on working memory. An alternative site for
15 this electrode would pass into CeM to modulate orbitofrontal cortical activations. The approach could be optimized based on other considerations, such as safety of entry point.

After placement of the electrode(s) in the
20 operating room, activation of the right Cm-Pf stimulator elicits spontaneous left arm movements. While no similarly dramatic behavioral change is noted with the left Pc/CL/paralamellar MD stimulator, scalp EEG electrodes monitored by a digital-EEG with spectral
25 displays show increased high frequency activity over the left prefrontal cortex. The stimulators are left in place and the patient is brought to rehabilitation. It is predicted, based on increased attentional and working memory capacity along with improved spontaneous movement
30 and left-sided motor control, that the patient will demonstrate increased capacity to perform activities of daily living.

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Example 3 -- Reintegration of Impaired Cortical Regions
By Vestibular Stimulation

An 81 year old, right handed woman suffered an acute left hemispheric cerebral infarct following an elective
5 repair of an aortic aneurysm. The patient had recovered to a point of ambulating and was scheduled for discharge to a rehabilitation facility. At 1800 hours on post-operative day 23, she was found lying sideways on her bed unable to talk or move her right side. Vital signs were
10 within the normal range with the exception of an elevated blood pressure of 175/90. On initial neurologic examination, she was awake and globally aphasic. Her eyes were fully deviated to the left at rest. This dense left lateral gaze preference could not be overcome by passive
15 rotation of the head. The appearance of a right visual field cut (homonymous hemianopia) was noted as the patient did not blink to visual threat from the right side. Right sided strength was markedly reduced (graded 1/5 in the upper extremity, 3/5 in the proximal lower
20 extremity and 2/5 in the distal lower extremity). She withdrew from noxious stimuli bilaterally. Deep tendon reflexes were brisk and symmetric. Right plantar response was extensor. The general medical exam was unremarkable. CT scan of the head revealed no hemorrhage or or early
25 signs of a structural lesion. She was given aspirin and no further intervention. At 2000 hours she was able to make gross movements of the right arm, lift the right leg and answer questions with brief 1-2 word answers.

At 2230 hours she was awake, alert with a moderate
30 expressive aphasia and a notable receptive aphasia. A dense right hemispatial neglect was noted. Eye deviation

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to the left was evident at rest and leftward eye movements were noted in response to auditory stimuli emanating from the right side. She was unable to visually track past the midline and demonstrated a loss of

5 response to visual threat from the right accompanied by unawareness of any right-sided stimuli when queried. Optokinetic nystagmus was elicited with bars moving to the left, but not to the right. An object-referenced visual extinction of one of two moving finger stimuli was

10 noted within the left hemi-field. Depending on the head position of the examiner, i.e., leaning in from the right or left side of the bed and testing the left visual field with outstretched hands each with a moving finger, the patient extinguished either the lower finger (examiner's

15 head tilted 90 degrees from the left side) or the upper finger (examiner's head tilted 90 degrees from the right side). The patient's right hand and arm were tightly held against the side of her chest and exhibited no spontaneous movements. When this hand was moved with

20 effort and brought into the left visual hemi-field the patient could not identify the hand as her own. Asked, "whose hand is this?" the patient tentatively replied, "I don't know" and further denied the hand as her own when queried.

25 After otological exam revealed normal tympanic membranes and clear external auditory canals, the right external auditory canal was irrigated with 50cc of ice water. Within 30 seconds she underwent notable functional improvement. She immediately oriented both head and eyes

30 to right sided auditory cues and held visual attention to the right hemi-space. Object-referenced neglect was no

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longer evident in the left hemi-space. Simultaneous with the change in her response to auditory and visual cues in right-hemisphere, spontaneous 'exploratory' movements of the right arm and hand appeared. When the right arm was
5 presented to the patient with the question "whose hand is this?", she now replied immediately and with emotional emphasis, "That's my hand!" During the following four minutes, the patient slowly relapsed her resting body, head, and eye positions back toward her post-stroke
10 baseline.

A 1.5 Tesla MRI scan obtained 24 hours after the stroke demonstrated multiple cortical infarcts with distribution of emboli from a proximal region of the middle cerebral artery. The left temporal lobe was most
15 uniformly affected along with frontal, parietal and occipital ischemic regions. T2 weighted MRI axial imaging demonstrated hypodense lesions consistent with infarctions of the temporal lobe. A thallium SPECT examination showed normal regional cerebral perfusion to
20 the left temporo-parietal occipital region and minimal reduction of blood flow in the contralateral cerebellum suggesting a mild reversed crossed cerebellar diaschisis phenomenon. Stroke evaluation was unremarkable including a normal carotid Doppler exam and echocardiogram. A
25 repeated attempt with caloric stimulation on post-op day 30 elicited less recovery than the first stimulation. The reduced effect observed at this later examination likely reflects a further loss of cortical tissue due to the filling in of the penumbra of the stroke filled in over
30 the hours and few days following the initial examination. However, a similar pattern of improvement was evident

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with improved hemi-spatial localization of auditory and visual stimuli and movements of the right arm. At this point the patient did not consistently exhibit object-referenced neglect or asomatognosia at baseline. The
5 patient remained with a dense right-sided neglect and mild right sided weakness and was transferred to a nursing home on post-operative day 31.

Although the invention has been described in detail for the purpose of illustration, it is understood
10 that such detail is solely for that purpose, and variations can be made therein by those skilled in the art without departing from the spirit and scope of the invention which is defined by the following claims.

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WHAT IS CLAIMED:

1. A method for treating a conscious patient having impaired cognitive function, said method comprising:

selecting a conscious patient with impaired cognitive function; and

applying electrical stimulation to at least a portion of the patient's intralaminar nuclei under conditions effective to relieve the patient's impaired cognitive function.

2. A method according to claim 1, wherein the patient does not suffer chronic pain.

3. A method according to claim 1, wherein the patient does not suffer from generalized seizures.

4. A method according to claim 1, wherein the patient does not suffer chronic pain and does not suffer from generalized seizures.

5. A method according to claim 1, wherein the at least a portion of the patient's intralaminar nuclei does not include the centromedian-parafascicularis or the central lateral.

6. A method according to claim 1, wherein the patient's impaired cognitive function can be modulated by external or internally generated stimulation.

7. A method according to claim 1, wherein the patient exhibits spontaneous fluctuations in cognitive function impairment.

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8. A method according to claim 1, wherein the at least a portion of the patient's intralaminar nuclei comprises paralamellar regions.

9. A method according to claim 1, wherein electrical stimulation is applied only to the at least a portion of the patient's intralaminar nuclei.

10. A method according to claim 1, wherein the patient exhibits deficits of attention, intention, working memory, or awareness.

11. A method according to claim 1, wherein the patient's impaired cognitive function is, at least partially, the result of a brain injury produced by stroke, blunt head trauma, missile penetration, toxicological agents, anoxia, ischemia, nutritional deficiencies, developmental diseases, degenerative diseases, infectious diseases, neoplastic diseases, or complications thereof.

12. A method according to claim 1, wherein the patient has a specific cognitive function impairment, wherein said method further comprises:

selecting a subdivision of the patient's intralaminar nuclei which modulates the specific cognitive function, and wherein said electrical stimulation is applied to at least the selected subdivision.

13. A method according to claim 12, wherein electrical stimulation is applied only to the selected subdivision.

14. A method according to claim 12, wherein said selecting comprises:

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determining an area of the brain having reduced baseline function; and

correlating the area of the brain having reduced baseline function with an intralaminar nuclei subdivision which projects thereto.

15. A method according to claim 14, wherein the area of the brain having reduced baseline function exhibits increased function during periods of patient activity.

16. A method according to claim 14, wherein electrical stimulation is applied only to the selected subdivision.

17. A method according to claim 14, wherein said determining is carried out metabolically, physiologically, or anatomically.

18. A method according to claim 1, wherein said applying electrical stimulation comprises:
contacting the at least a portion of the patient's intralaminar nuclei with an electrode under conditions effective to deliver an electrical signal to the at least a portion of the patient's intralaminar nuclei.

19. A method according to claim 18, wherein the electrode is capable of delivering pharmacological agents to the at least a portion of the patient's intralaminar nuclei.

20. A method according to claim 1, wherein electrical stimulation is applied continuously.

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21. A method according to claim 1, wherein electrical stimulation is applied intermittently.

22. A method according to claim 1, wherein electrical stimulation is applied periodically.

23. A method according to claim 1, wherein electrical stimulation is applied to two or more subdivisions of the intralaminar nuclei which modulate separate cortical regions.

24. A method according to claim 23, wherein electrical stimulation is applied periodically.

25. A method according to claim 23, wherein electrical stimulation applied to the two or more subdivisions of the intralaminar nuclei is synchronized.

26. A method according to claim 23, wherein at least one of the two or more subdivisions of the intralaminar nuclei lies in the right thalamus and at least one of the two or more subdivisions of the intralaminar nuclei lies in the left thalamus.

27. A method according to claim 23, wherein the patient has a specific cognitive function impairment and wherein at least one of the two or more subdivisions of the intralaminar nuclei modulates the specific cognitive function.

28. A method according to claim 23, wherein the patient has a specific cognitive function impairment and wherein at least two of the two or more subdivisions intralaminar nuclei modulates the specific cognitive function.

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29. A method according to claim 1, wherein said method produces regional or intrahemispheric changes in brain waves.

30. A method according to claim 1 further comprising:

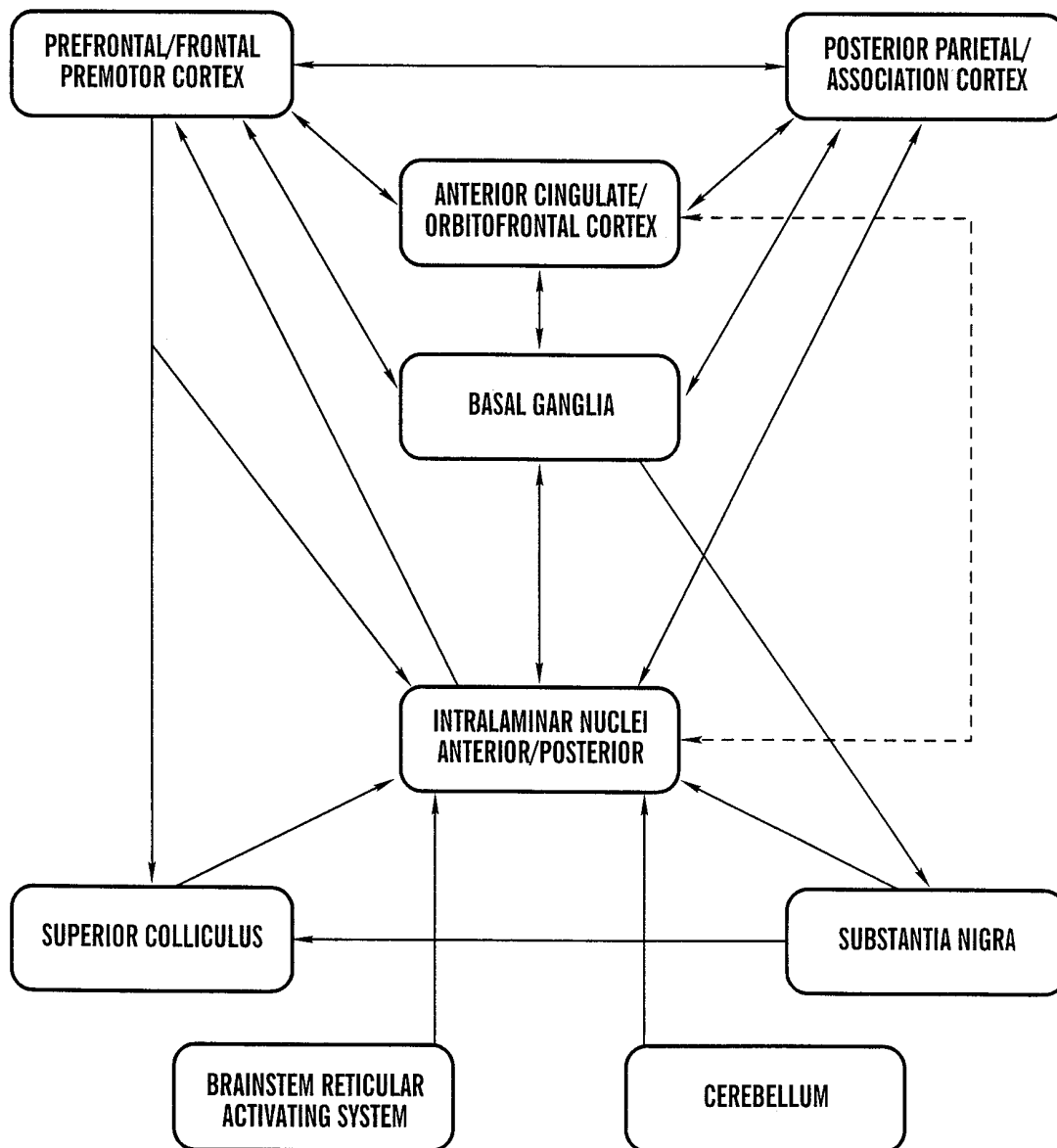
contacting the at least a portion of the patient's intralaminar nuclei with a pharmacological agent.

31. A method for improving coordination of function across cortical regions in a patient comprising:
applying electrical stimulation to two or more subdivisions of the patient's intralaminar nuclei, wherein the two or more subdivisions of the patient's intralaminar nuclei modulate separate cortical regions.

32. A method according to claim 31, wherein electrical stimulation applied to the two or more subdivisions of the intralaminar nuclei is synchronized.

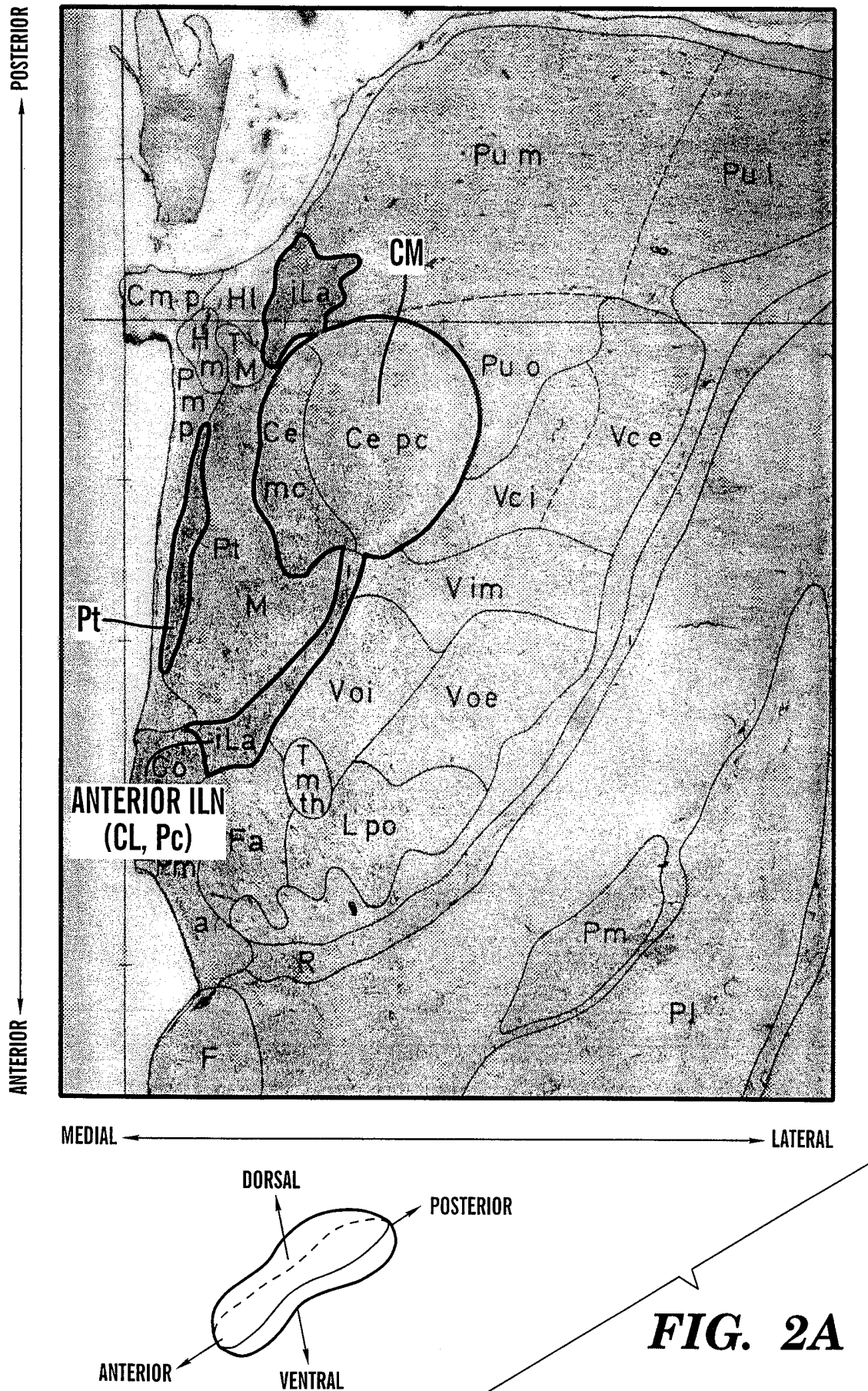
33. A method according to claim 31, wherein electrical stimulation applied to the two or more subdivisions of the intralaminar nuclei is periodic.

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**FIG. 1**

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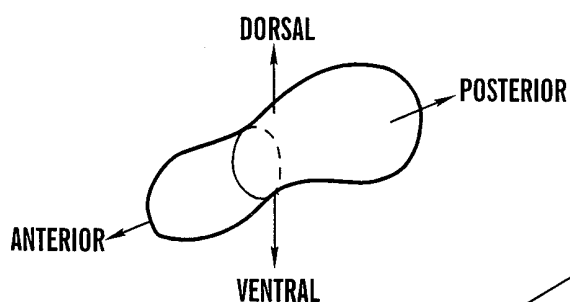
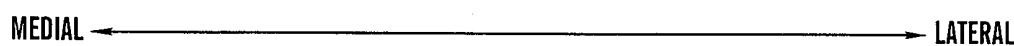
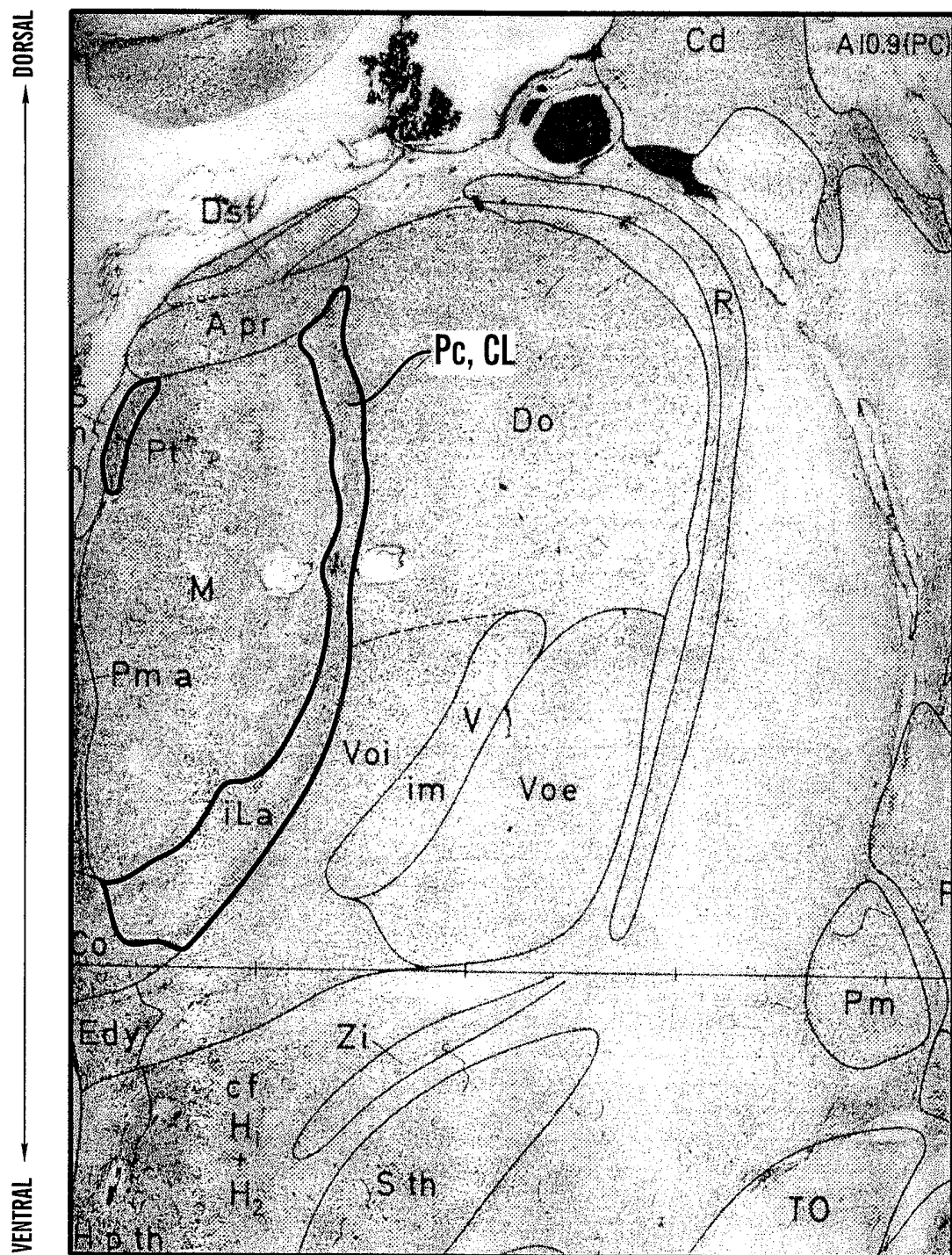
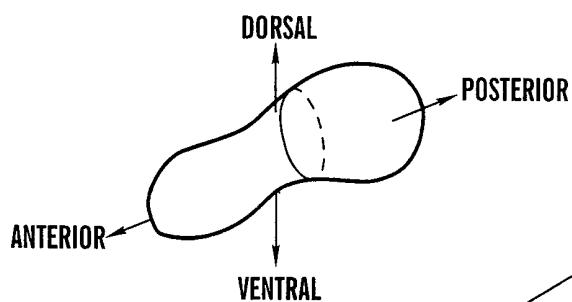
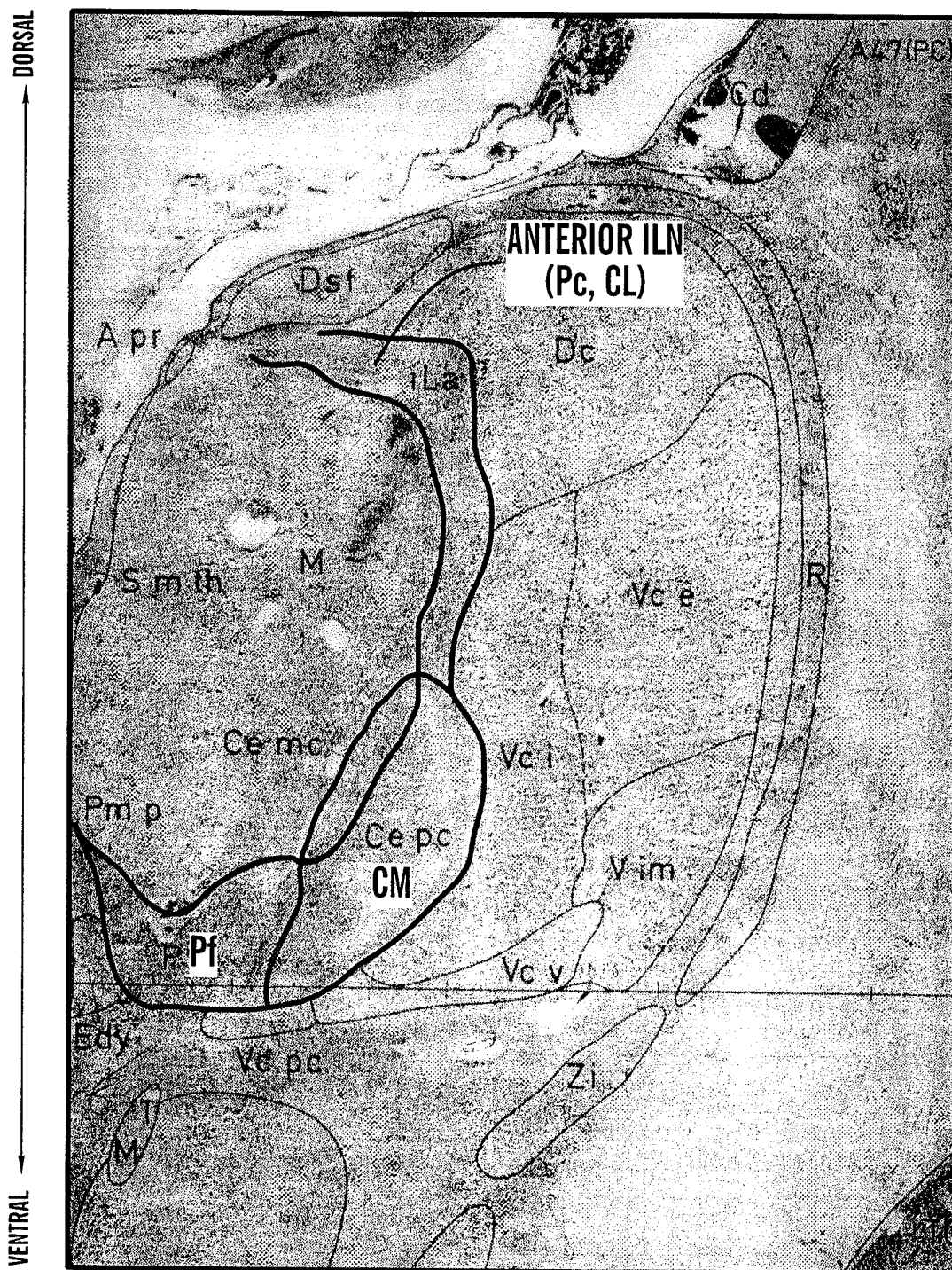


FIG. 2B

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**FIG. 2C**

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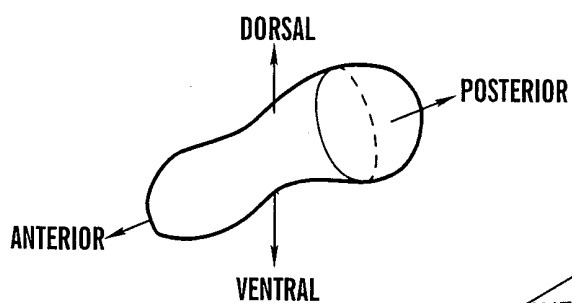
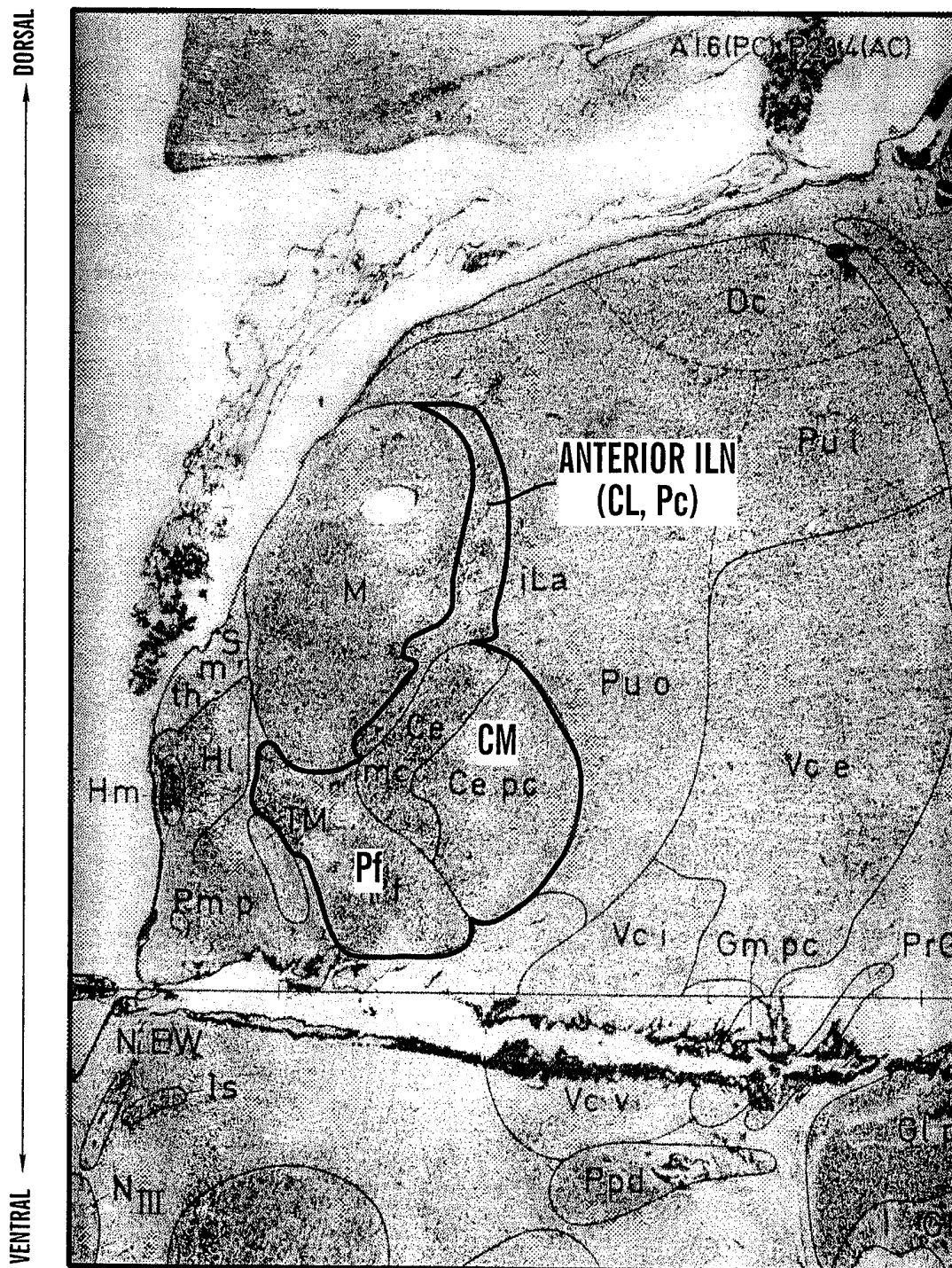
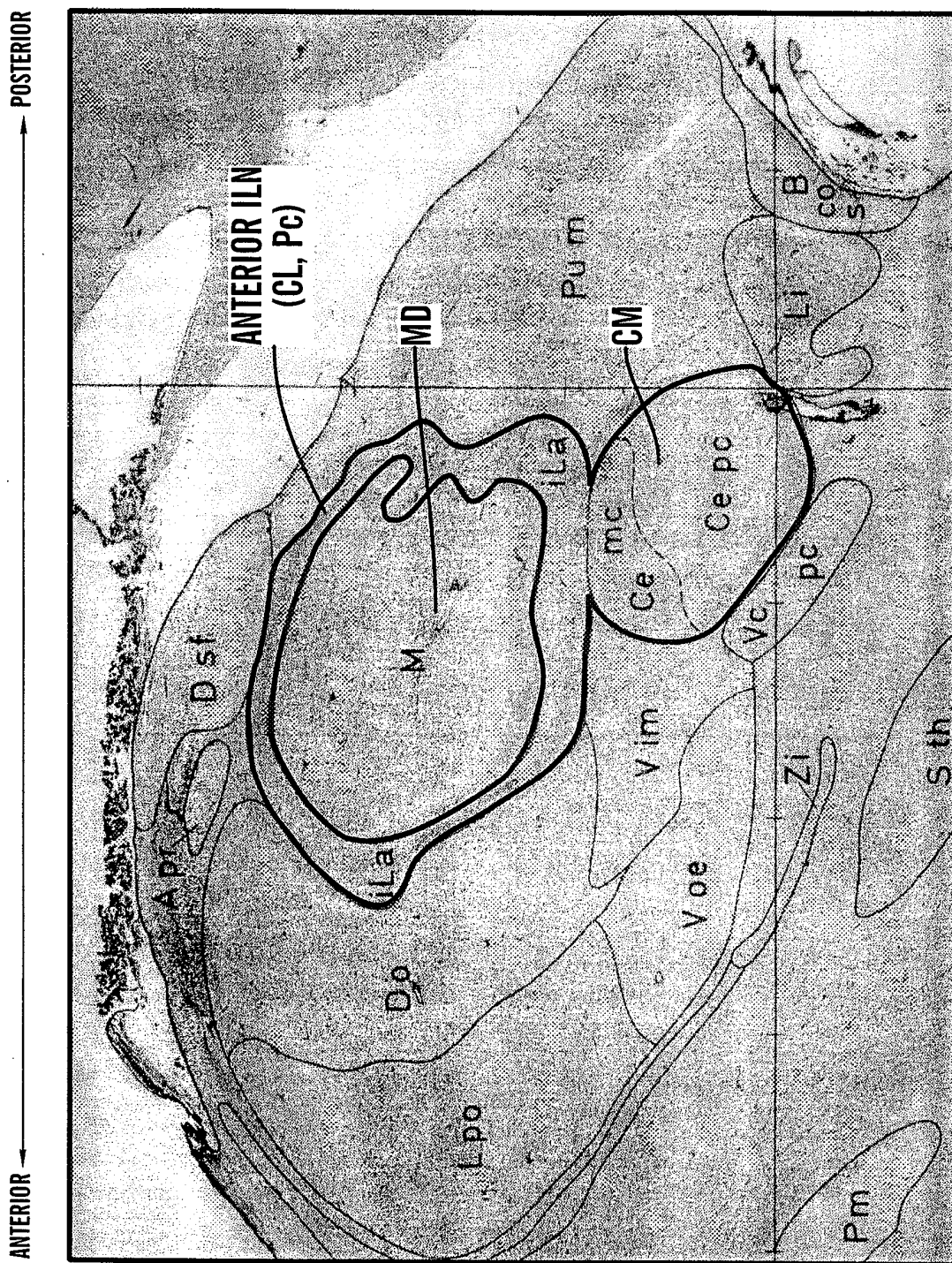


FIG. 2D

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ANTERIOR POSTERIOR DORSAL VENTRAL

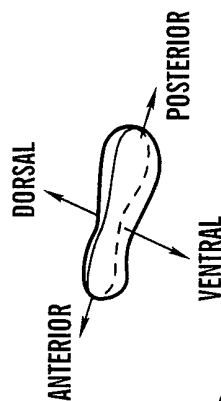


FIG. 2E

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/21935

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61N 1/36

US CL : 607/045

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 607/045, 116

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| A | US 5,269,303 A (WERNICKE et al) 14 December 1993. | 1-33 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | |
|---|--|
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| *O* document referring to an oral disclosure, use, exhibition or other means | |
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Date of the actual completion of the international search

24 NOVEMBER 1998

Date of mailing of the international search report

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