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RESEARCH ARTICLE

A New Approach to Tumor Cancer with a Novel Imaging Profile for White matter abnormalities including Leukodystrophies: Sensing the Human Brain

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ABSTRACT

Neuromolecular Imaging (NMI) for white matter detection, distinct from that of gray matter is an inventive art. (1) This imaging technique demonstrates, for the first time, a LIVE and continuous videotracking nanotechnology for distinguishing white matter from gray matter in the brain of epilepsy patients, online, in real time and for long periods of time. NMI is known to perform with unrivaled temporal and spatial operational reliability and reproducibility Thus, a nanotechnology for white matter disorders, for example, leukodystrophies, is published for the first time. The purpose of this paper is to present a critical distinction for white *versus* gray matter in hippocampal and neocortical resected tissue derived from mesial and neocortical temporal lobe epilepsy patients *en bloc* during intraoperative surgery; the patients present as medically refractory to classical pharmacotherapeutics. The tiny carbon-based lipid polymeric sensor, the BRODERICK PROBE® readily sees white matter in contrast to gray matter in brain neuroanatomic substrates as it continually senses the glia or the neuron, white or gray matter, respectively, with distinct clarity *via* electroactive signal processing. The difference between white and gray matter is striking as the videotrace slides smoothly from the white to the gray milieu. Thus, a primary *in vivo* white matter nanotechnology is presented to advance diagnosis and therapy for white and gray matter abnormalities in the brain and spinal cord.

Keywords: brain, spinal cord, electrical circuits, white matter, gray matter, leukodystrophies, multiple sclerosis, amyotrophic lateral sclerosis, ascorbic acid, dopamine, serotonin, norepinephrine, myelin, tumors, glia, epilepsy, surgery, patients, seizure, imaging, biomedical engineering, sensors, biosensors, nanotechnology

INTRODUCTION

Myelin makes up most of the substance of white matter in the central nervous system but there is a composition of gray matter also, that is, gray matter, unmyelinated fibers, surround the deeper white matter. Gray matter makes up the outer most layer of the brain; it is thin, about 2-4 mm. The hippocampus and the neocortex, about which this article centers, are each comprised of white and gray matter. Too, gray matter contains a high concentration of neuronal cell bodies, dendrites whereas white matter, is comprised primarily of myelinated white matter known as glia. The Band of Baillarger, Layer IV, is a layer of white matter coursing through the gray matter and this band separates the temporal lobe from the temporal brain stem; The Broderick probe is a patented nanoprobe and one of its unique properties is to clearly distinguish white matter from gray matter readily and reliably, with superior temporal and spatial resolution, within seconds in human brain. (1) In this article, we focus on the epilepsy patients.

The BRODERICK PROBE® sensors (*named after the PI's father*) relate to several formulations of unique, patented, and trademarked miniature carbon sensors comprising a series of compounds which include, among others, classes of molecules in the biochemical categories of lipid, glycolipid, lipoprotein, saturated and unsaturated fatty acid. These inventions are able to detect electrochemical signals for a vast number of neurotransmitters, neuromodulators, and metabolites, including neuropeptides. We continue to pioneer and develop new biosensors comprised of new formulae. The molecular approach of the BRODERICK PROBE® as it relates to tumor cancers is discussed (15), in chapter 13, in press. Electroactive images for white matter in contrast to gray matter are seen in the results section.

METHODS

Novel biosensors:

Fig. 1

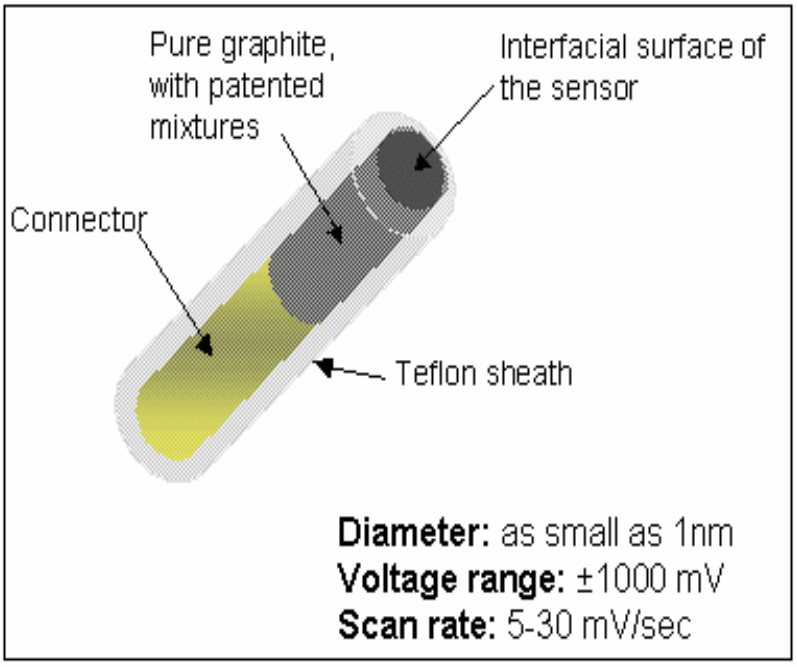

Figure 1: Schematic drawing of the BRODERICK PROBE® sensor

The sleek biosensor, BRODERICK PROBE® sensor, also called a nanoprobe is smaller than a human and it is designed to diagnose, treat and find strategies to treat brain disorders. The nanoprobe is available for market production. This biosensor is a medical diagnostic and therapeutic device, comprised of biologically compatible materials, capable of imaging neurotransmitter signals directly from the brain actually during movement. during the natural state, the diseased state and the medically/surgically treated state *in the same subject in real time*. It is the first biosensor in the world that is capable of, video-tracking "visualizing" brain neurotransmitters as signals for each neurotransmitter are seen in real time on computer or mobile device. This biosensor is patented for clinical and preclinical use in humans and animals. (1,13) This biosensor images the brain, opens the brain without opening the brain and does not harm the brain. (14) This biosensor/nanoprobe does not produce bacterial infection in long term studies and unlike other sensing devices, the Broderick nanoprobe has proven to be successful in the patient without producing scar tissue.

The signature for the biogenic amines, dopamine (DA) serotonin (5-HT) and norepinephrine (NE) and for the catalytic vitamin, ascorbate (AA), is empirically determined *via* the redox potential for each neurochemical; these digital values are experimentally derived by assaying each neurochemical *in vitro* in Ringer's Lactate and/or PO_4 Buffer.

In these studies, the BRODERICK PROBE® is placed (2 microns) within the neocortical neuroanatomic substrate, Layer IV derived from epilepsy patients *en bloc* and in separate studies, the placement of the nanoprobe sensor was within hippocampal tissue. The hippocampal subparcellations that were studied in twelve of fourteen epilepsy patients were (a) granular cells of the dentate gyrus (DG) (gray matter), (b) polymorphic layer of the Dentate Gyrus, the alveus (white matter), (c) the subiculum of the hippocampus (white matter) and (c) hippocampal pyramidal layer (gray matter). The white matter in temporal stem of neocortex was studied in the entire group of 14 patients studied.

METHODS

The progression and advancement of electrochemical technologies into Neuromolecular Imaging can be described in two parts.

- **In Vivo Electrochemistry**

Conventional Microvoltammetry: Conventional microvoltammetry involves the implantation of an indicator electrode and a reference electrode in specified regions of brain, the application of a potential to an indicator electrode, the oxidation or reduction (redox) reaction of selected neurochemicals, and the recording of current derived from that redox reaction. Information about analytes is provided as a function of the potential difference, as this potential difference activates the surface of the indicator electrode.

1. Involves measurement of current in an electrochemical cell as a function of applied potential.
2. Electroactive species undergo redox reactions at a characteristic redox potential.
3. The formula is: O + ne - $\Leftrightarrow$ R, wherein, ne = number of electrons, O = oxidation, R = reduction.
4. The amount of current that is produced is proportional to concentration: the Cottrell equation.

Methods based on conventional voltammetry and microvoltammetry have validated that the flow of charge, i.e., amount of current in amperes, which passes through the surface of an indicator electrode is proportional to the concentration of the electroactive species studied. The following formulas describe this relationship in terms of charge, electron transfer, current, diffusion layer, time, Faraday's constant, size of the indicator electrode and concentration (mass) of electroactive species.

$$Q = nFVC_{oR}$$
$$i = dQ/dt$$
$$i = nFVdC_{R,t}/dt$$

where V is the volume of the diffusion layer on the electrode where the measurement is being made, n is the number of electrons transferred, F is the Faraday constant, and C_o denotes initial concentration. The Cottrell equation is derived from the formulas written above and demonstrates that current, i.e., charge, and mass, i.e., concentration, are proportional.

- Neuromolecular Imaging (NMI)

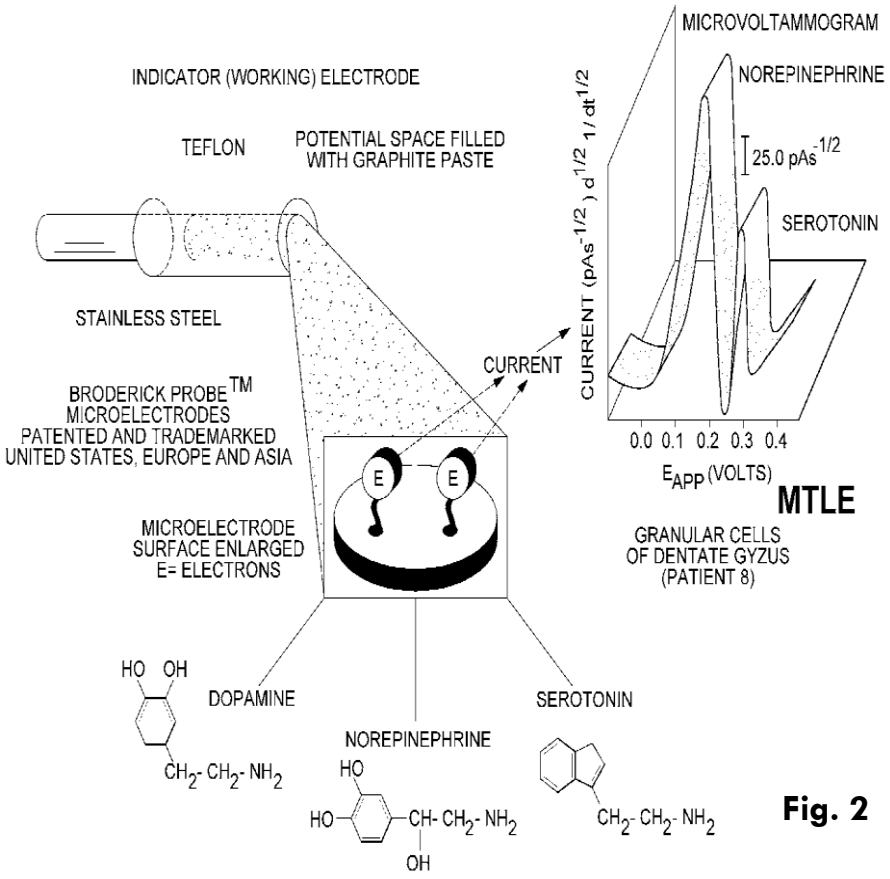

Fig. 2

Figure 2: The electromechanics of the BRODERICK PROBE® sensor. **MTLE-** Mesial Temporal Lobe Patient

We have a novel biotechnology which uses conventional microvoltammetry as its basis. In this paper, as described under "Recordings and Circuits," Neuromolecular imaging (NMI) utilizes a semiderivative voltammetric circuit to apply a potential difference to a sensor. In essence, the potential is applied between the indicator and the reference electrode wherein the indicator electrode reads current and the reference electrode provides a relative zero potential. The term voltammetry denotes a specific electrical circuit, and there are several different types of circuits, by which a potential difference can be applied to the nanoprobe. It should be noted that the term, voltammetry does not define neurotransmitter selective nanoprobes, nor does voltammetry denote the detection or imaging of neurotransmitters. NMI, on the other hand, includes detection and imaging of neuromolecules. Thus, a significant difference between conventional microvoltammetry and NMI is the development of new sensors and nanoprobes to image neurotransmitters within seconds over long periods of time, *in vivo, in vitro*, and *in situ*.

- ***Recordings and Circuit***

Within seconds, ascorbate, DA, and 5-HT, each at distinct and separate signature oxidation potentials, were selectively recorded. Each neurochemical was detected in 10 sec. Repetitive scanning took place every 2 min for 1 to 2 h in an electrochemical cell for *in vitro* studies. For *in vivo* studies in the animal and human brain, repetitive scanning took place according to protocol. Charging (background) current was recorded and eliminated in the first 20 sec of each recording. For these studies, a semiderivative circuit was used; this circuit provides the first half-derivative of the analog linear signal. A semiderivative circuit combines an additional series of resistors and capacitors, called a "ladder network" with linear scanning circuits and the addition of this "ladder network" to the linear scanning circuit records sharper, more defined peaks. Presently, computerization and the remote-control features for NMI imaging are performed with an Autolab (Brinkmann Inc., Westbury, NY).

- **Patient Classification**

~~Thirteen~~ consecutive patients who had temporal lobe resections for intractable seizures were studied. Four patients, 2 males and 2 females ages 36.75 ± 8.4 years were classified as having neocortical temporal lobe epilepsy (NTLE) based on the lack of hippocampal (HPC) atrophy on MRI and tissue examination, in addition to demonstrating seizure onset in temporal neocortex during chronic intracranial electroencephalographic (EEG) studies with lateral temporal subdural grid electrodes and multiple baso-mesial temporal sub-dural strip electrodes. Patients were classified as having mesial temporal lobe epilepsy (MTLE) if pathologic examination of the resected temporal lobe revealed severe hippocampal neuronal loss and gliosis and if examination of the neocortex revealed no other etiology for the patient's epilepsy. Nine patients (4 males and 5 females, ages 31.4 ± 3.9 years) were classified as MTLE based on these features.

Prior to implantation of intracranial electrodes, i.e., subdural grid and strip electrodes (AdTec Inc., Racine, Wisconsin), all patients had presurgical evaluations that included audiovisual and EEG monitoring of interictal and ictal activity, magnetic resonance imaging (MRI) with 3-mm coronal cuts through the temporal lobes, a neuropsychological evaluation and angiogram-Wada testing. Patients were referred for intracranial EEG monitoring after a review of the presurgical evaluation by a multi-disciplinary epilepsy team of neurologists, neurosurgeons and neuropsychologists. Functional mapping of cortex was performed in patients with dominant hemispheric seizure foci, using a Grass Instrument S-12 stimulator.

Therefore, four patients were classified as NTLE and nine patients were classified as MTLE based on MRI and intracranial EEG evaluations. Neuromolecular Imaging was used to subtype tissue samples according to the neurochemistry of biogenic amines. (2,3) We have imaged both the epilepsy brain intraoperatively as well as resected tissue in epilepsy patients. (4) A precise explanation for the role of ascorbate in the subtyping procedure is reported. (5) NMI and the BRODERICK PROBE® library of nanosensors and nanobiosensors are described in detail. (6) A textbook of conventional electrochemistry is provided by Kissinger. (7) A textbook for Neuromolecular Imaging is provided by Broderick. (15). NMI primarily but not exclusively detects release mechanisms for neurotransmitters as shown by γ-butyrolactone studies. [8]

RESULTS

Neuromolecular Imaging in Epilepsy Patients Intraoperatively

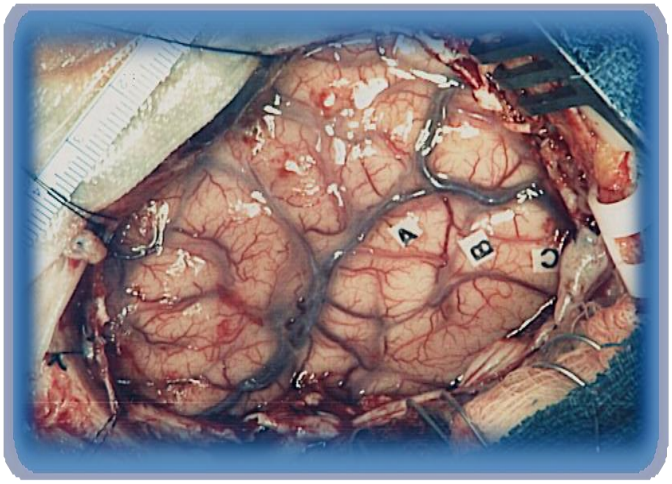

Figure 3: Anterior temporal lobe of the epilepsy brain LIVE during intraoperative surgery.

Neuromolecular Imaging in Epilepsy Patients *In Situ* in Resected Tissue *en bloc*

The Hippocampus of the Epilepsy Patient

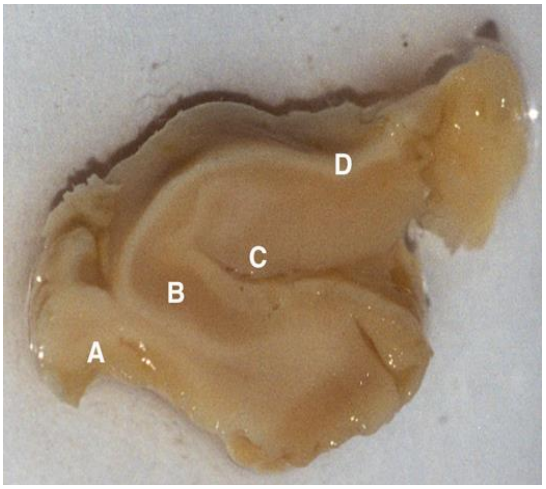

Figure 4: A longitudinal section of the hippocampus resected *en bloc* just prior to NMI.

KEY:

A. Subiculum;
B. Pyramidal cell layer
C. Granular cell layer of the Dentate Gyrus (DG)
D. Alveus.

The Temporal Neocortex of the Epilepsy Patient

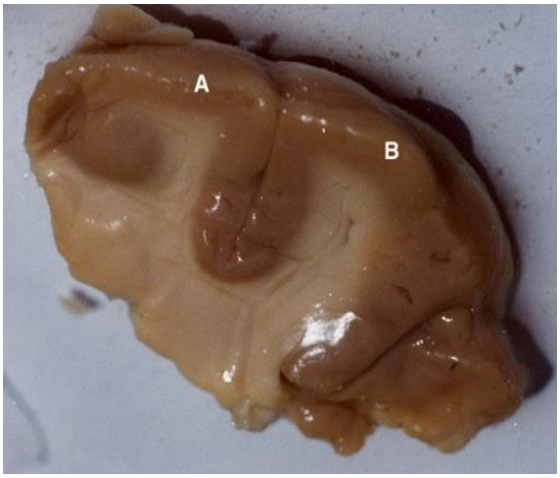

Figure 5: A section of the anterolateral temporal neocortex through the inferior and middle temporal gyrus. A, inferior temporal gyrus; B, middle temporal **gyrus.**

White and Gray Matter Signal Processing with NMI and the BRODERICK PROBE® (1)

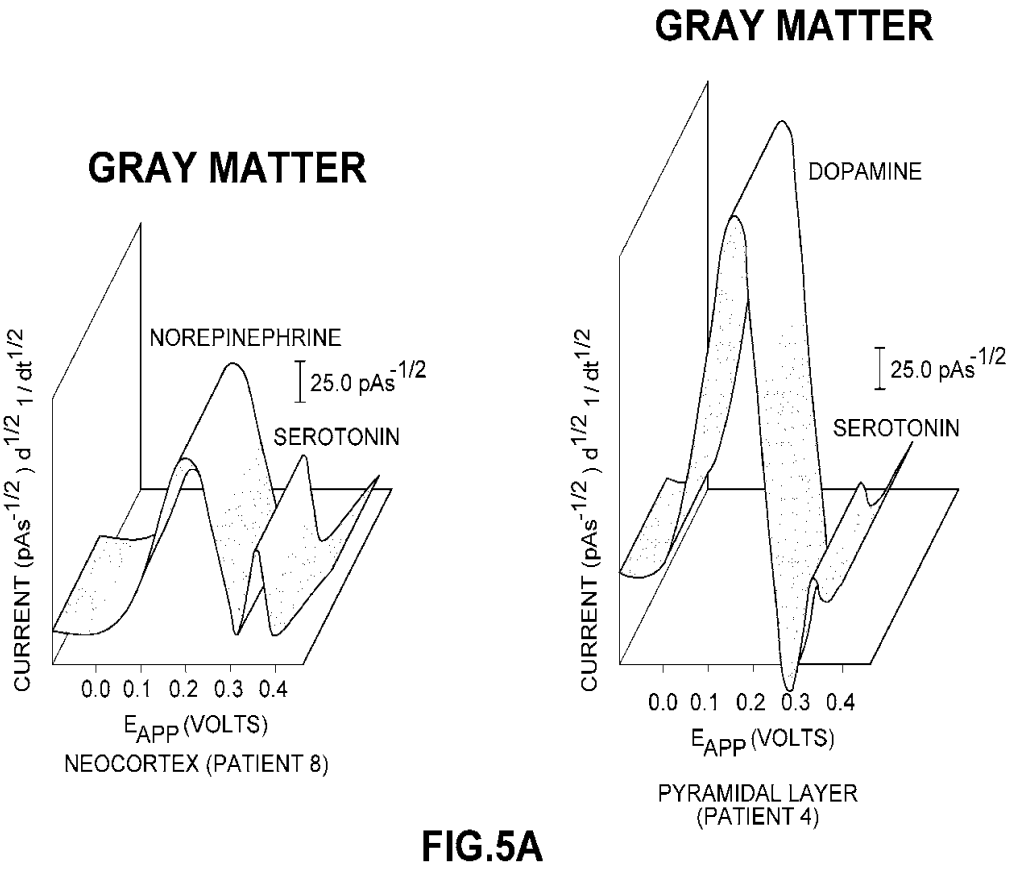

FIG.5A

Figure 5A: Gray to Gray Matter: Neuroanatomic Substrates, *Neocortex (White Matter) and Pyramidal (Gray Matter) show* LIVE profiles with sharp electroactive signals for norepinephrine and dopamine with sharp indoleamine signals for serotonin. Patient profiles are demonstrated for patient 8 and patient 4. Gray matter catecholamine and indoleamine signaling exhibits high adsorption values in gray matter within the neocortex. Thus, the profile on the left for patient 8 shows gray matter within the neocortex, comprised of white and gray matter. Patient 8 profiles gray matter within gray matter. This is a revolutionary finding. That such specificity is enabled by the tiny probe and yet, the nanoprobe is **not** bulky and is affordable, is unique with those of the indoleamine signaling. A biomarker for white matter within gray matter signaling processing is enabled by NMI and the Broderick nanoprobe. **This is the first time that the profiles, shown herein are published in journal form. The profiles are striking in their specificity to diagnose and treat white matter distinct from gray matter in patients.**

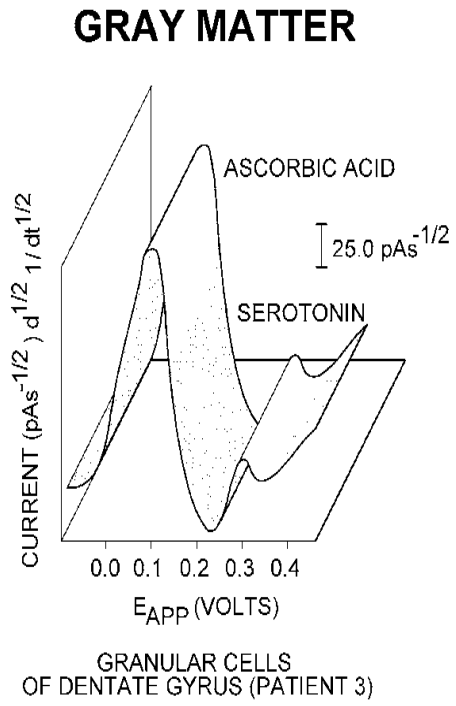

FIG.5A (CONTINUED)

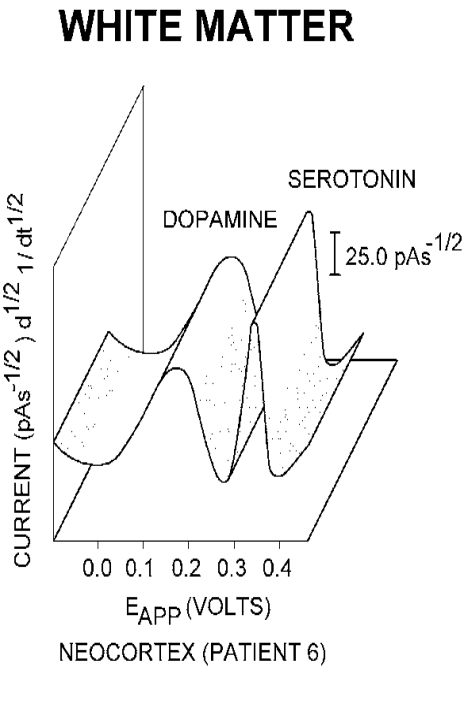

FIG.5B

Figure 5A to 5 B: Gray to White Matter: Neuroanatomic Substrates, *Granular Cells of the Dentate Gyrus (Gray Matte)* shows a sharp electroactive signal for ascorbate in gray matter of a primarily gray matter substrate albeit the hippocampal substrate is comprised of white matter as well. The profile is that of patient 3. In patient 6, the results show a diffuse electroactive dopamine signal in **white matter within the white matter substrate, the neocortex and similarly to hippocampus, the neocortex is comprised of both white and gray matter.** The serotonin signaling is dramatically sharper than is dopamine, the catecholamine signal processing in **white matter in neocortex.** Biomarkers are introduced for white matter distinct from gray matter both preclinically and clinically **Abnormalities for white matter as well as for gray matter are enabled with the Broderick novel nanoprob**e. **This work is revolutionary, enabling preciseness without cumbersome and expensive machines.**

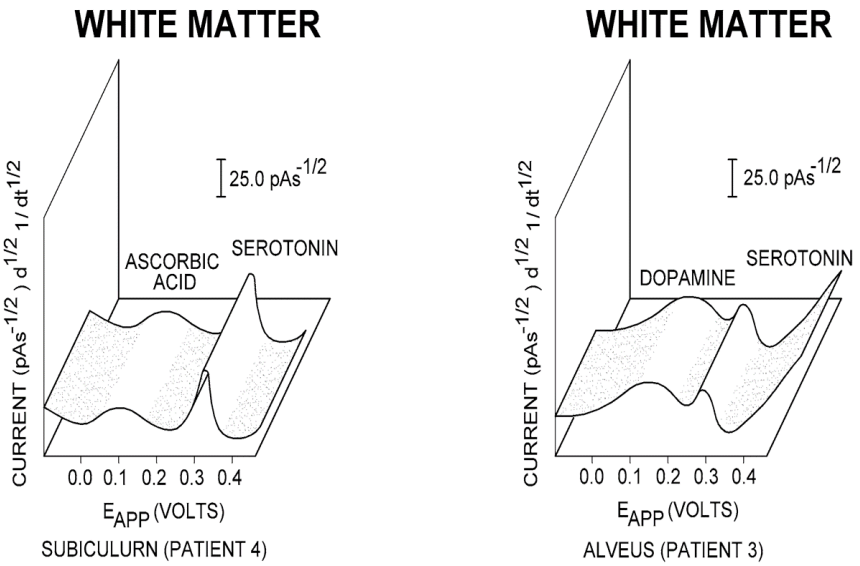

FIG.5B (CONTINUED)

Figure 5B continued: White to White Matter: Neuroanatomic Substrates, *Subiculum* and *Alveus*. These are both white matter substrates that are hippocampal! White matter in subiculum is imaged in patient 4 and the LIVE image shows diffuse electroactive signals for ascorbate as well as for dopamine in patient 3 with sharp indoleamine, serotonin, electroactive signals in patients 4 and 3. White matter signaling provides biomarkers for serotonin indoleamine peaks that are higher in amplitude **and concentration** than are catecholamines and/or ascorbate in white matter. Indole dipole attraction by carbon enables serotonin adsorption to a greater extent than dopamine or norepinephrine, the catecholamines. (9) The biogenic amines are characterized according to redox potentials. (10,11) The data provide new technologies for detection of white distinct from gray matter in either white or gray matter abnormalities. The approach that the novel nanoprobe uses brings new technologies and nanotechnologies to the world, enabling advanced future therapies that respectfully lead beyond MRI with Diffusion Tensor techniques. (12)

DISCUSSION

White matter imaging devices using functional magnetic resonance imaging (fMRI) with diffusion tensor techniques (DTI) with equations for isotropy and anisotropy are known. It is interesting that the BRODERICK PROBE® and Neuromolecular Imaging (NMI) was discovered and published in patent form at the same time that fMRI with DTI was introduced into clinical use. An example of fMRI with DTI as shown in a patient with multiple sclerosis is reported. (12) We introduce NMI with the BRODERICK PROBE® for use alone as well as with the fMRI/DTI imaging technologies. In fact, the semiconductor properties of the carbon allotrope, BRODERICK PROBE® fullerene nanosensor used with fMRI/DTI predicts faster fMRI, DTI signals. (13)

NMI and the BRODERICK PROBE® uses lipid biomimetics to provide a faster, continuously noninvasive and economical way to image white matter distinct from gray matter in patients with white matter disease such as multiple sclerosis and leukodystrophies as well as in patients with epilepsy. Both the nanobiosensors and myelinated white matter in the brain and spinal cord are electronic devices that bond in the polymeric nanoprobe due to such factors as lipid biomimetics and lipophilicity, discussed in the innovative textbook. (15) Strong adsorption properties between the tiny probe and the brain's myelinated white matter enable a novel approach and advanced nanomaterials to current technologies, for example, MRI. The findings show that white matter signals *versus* gray matter signals are not dependent on NTLE or MTLE subtypes. Since white matter detection by NMI is an inventive art poised and ready for the clinic, the author wishes to delineate the differences and similarities for NMI and DTI to further understand MRI technology as compared with NMI nanotechnology and what each

can and do offer. Thus, a comparison of NMI with MRI follows,

- **NMI**

In NMI, action potentials are not involved; it is not a depolarization technology. It is important to note that these miniature sensors do not sense membrane potentials. These sensors pass small but finite currents while neurotransmitters close to the surface undergo oxidation and/or reduction). The current, which is formed from this flow of electrons, is dependent on voltage according to Ohm's law. Thus, the detection of electrochemical or electroactive signals from neuroanatomic brain sites is termed *faradaic* because the amount of the oxidative and/or reductive species detected at the surface of the microelectrode surface is calculated by a derivation of Faraday's law, which is the Cottrell equation.

- **MRI**

In MRI, action potentials are not involved; MRI is not a depolarization technology. Therefore, this property is similar to NMI. However, it is important to note that **in MRI as well as NMI with DTI**, as myelination occurs, there is a loss of water within the myelin sheath which decreases proton density, thus, enhancing the T1- weighted image and reducing the T2-weighted image. Too, signal changes on T1-weighted MRI patterns parallel increases in lipids that occur during myelin formed from oligodendrocytes. Signal changes on T2-wighted MRI patterns may correlate with the period of maturation of the myelin sheath. In MRI detection, hydrogen atoms of lipids do not contribute appreciably to the MR signal because hydrogen atoms of lipids are immobile
and bind tightly to long chain fatty acids. Instead, lipid protons affect MRI by interacting with the mobile water protons by, for example, chemical exchange with transiently immobilized water protons. Chemicals such as myelin-bound cholesterol and galactosecerebroside, of which the BRODERICK PROBE® are comprised, ~~are responsible for~~ endow shorter T1/T2-weighted relaxation times for normal myelinated white matter on MRI with DTI.

- **NMI/MRI: Similarities and Differences**

It is of interest that neither NMI nor the MRI technologies use action potentials. Neither technology is a depolarization technique. Whereas T1/T2-weighted images in MRI signals white matter changes and the presence or absence of white matter, it is electron transfer in NMI with our sensors that signals white matter changes and the presence or absence of white matter. In addition, in MRI detection, the hydrogen atoms of lipids do not contribute appreciably to the MR signal. Lipid protons affect the MR signal in MRI indirectly by communicating with water protons. In NMI with our sensors, lipids act to enhance signals indirectly as well, by enhancing electron transfer for electroactive species. Finally, in both technologies, structural and chemical changes in axons, in addition to length of carbon chain in fatty acids, and properties such as hydrophobicity and hydrophilicity, e.g., are significant factors, affecting and influencing the image and waveform patterns of white matter.

CONCLUSION

In summary, NMI with BRODERICK PROBE® nanobiosensors reliably differentiates temporal lobe gray from white matter in separate subparcellations of neocortex and hippocampus in Temporal lobe epilepsy (TLE) patients. These results have important implications for enabling direct *in vivo* measurement of neurotransmitters and critical analytes in diverse neuroanatomic substrates for producing temporospatial images of synaptic changes in TLE neuronal circuitry as well as others. The Broderick nanoprobe, trademarked the BRODERICK PROBE® enables more precise diagnosis of patients with white and gray matter abnormalities than ever previously marketed. It is said to be revolutionary. It is!

ACKNOWLEDGEMENTS

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