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(54) **Title:** TRANSCRANIAL MAGNETIC STIMULATION FOR ALTERING SUSCEPTIBILITY OF TISSUE TO PHARMACEUTICALS AND RADIATION

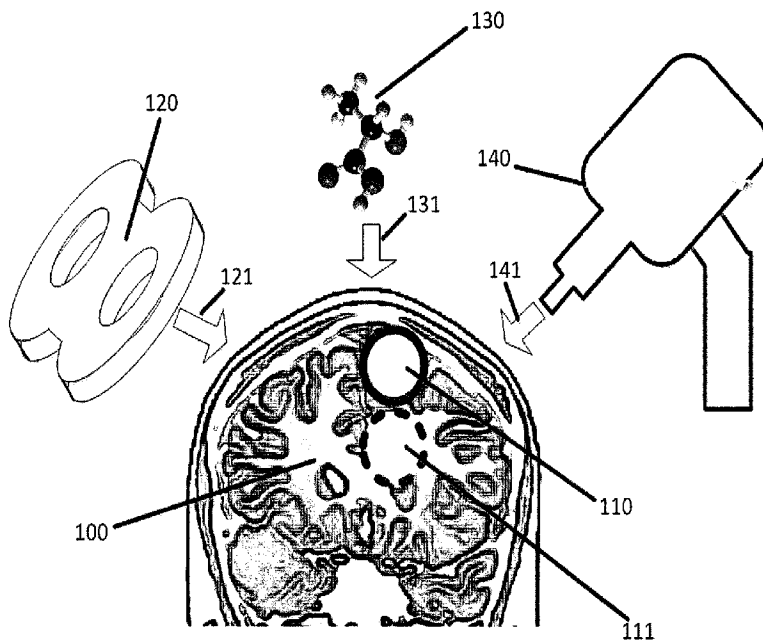


FIGURE 1

(57) **Abstract:** Described herein are methods for modulating the susceptibility of one or more target or tissue regions, and particularly one or more brain regions, to a therapeutic agent such as a drug, immune agent, compound, radiation, etc. In particular, the methods and systems described herein may include magnetic stimulation (including transcranial magnetic stimulation) of target or non-target regions to modulate the susceptibility of the one or more target or tissue regions to a therapeutic agent.

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**TRANSCRANIAL MAGNETIC STIMULATION FOR ALTERING SUSCEPTIBILITY
OF TISSUE TO PHARMACEUTICALS AND RADIATION**

CROSS REFERENCE TO RELATED APPLICATIONS

- 5 [0001] This patent application claims priority to provisional patent application serial number 61/365,025, titled "TRANSCRANIAL MAGNETIC STIMULATION FOR ALTERING SUSCEPTIBILITY OF TISSUE TO PHARMACEUTICALS AND RADIATION," filed on July 16, 2010.
- 10 [0002] This patent application may be related to one or more of the following patents and pending patent applications (US and PCT applications), each of which is herein incorporated by reference in its entirety: U.S. Patent serial No. 7,520,848, titled "ROBOTIC APPARATUS FOR TARGETING AND PRODUCING DEEP, FOCUSED TRANSCRANIAL MAGNETIC STIMULATION", issued on 4/21/09; U.S. Patent Application No. 12/402,404, titled "ROBOTIC APPARATUS FOR TARGETING AND PRODUCING DEEP, FOCUSED
- 15 TRANSCRANIAL MAGNETIC STIMULATION", filed on 3/11/2009; U.S. Patent Application No. 11/429,504, titled "TRAJECTORY-BASED DEEP-BRAIN STEREOTACTIC TRANSCRANIAL MAGNETIC STIMULATION", filed on 5/5/2006; U.S. Patent Application No. 12/669,882, titled "DEVICE AND METHOD FOR TREATING HYPERTENSION VIA NON-INVASIVE NEUROMODULATION", filed on 1/20/2010; U.S. Patent Application No.
- 20 12/671,260, titled "GANTRY AND SWITCHES FOR POSITION-BASED TRIGGERING OF TMS PULSES IN MOVING COILS", filed on 1/29/2010; U.S. Patent Application No. 12/670,938, titled "FIRING PATTERNS FOR DEEP BRAIN TRANSCRANIAL MAGNETIC STIMULATION", filed on 1/27/2010; U.S. Patent Application No. 12/677,220, titled "FOCUSED MAGNETIC FIELDS", filed on 3/9/2010; PCT Application No.
- 25 PCT/US2008/077851, titled "SYSTEMS AND METHODS FOR COOLING ELECTROMAGNETS FOR TRANSCRANIAL MAGNETIC STIMULATION", filed on 9/26/2008; PCT Application No. PCT/US2008/081048, titled "INTRA-SESSION CONTROL OF TRANSCRANIAL MAGNETIC STIMULATION", filed on 10/24/2008; U.S. Patent Application No. 12/324,227, titled "TRANSCRANIAL MAGNETIC STIMULATION OF
- 30 DEEP BRAIN TARGETS", filed on 11/26/2008; PCT Application No. PCT/US2009/045109, titled "TRANSCRANIAL MAGNETIC STIMULATION BY ENHANCED MAGNETIC FIELD PERTURBATIONS", filed on 5/26/2009; U.S. Patent Application No. 12/185,544, titled "MONOPHASIC MULTI-COIL ARRAYS FOR TRANSCRANIAL MAGNETIC

STIMULATION", filed on 8/4/2008; U.S. Patent Application No. 12/701,395, titled
"CONTROL AND COORDINATION OF TRANSCRANIAL MAGNETIC STIMULATION
ELECTROMAGNETS FOR MODULATION OF DEEP BRAIN TARGETS", filed on
2/5/2010; and PCT Application No. PCT/US2010/020324, titled "SHAPED COILS FOR
5 TRANSCRANIAL MAGNETIC STIMULATION", filed on 1/7/2010.

INCORPORATION BY REFERENCE

[0003] All publications, including patents and patent applications, mentioned in this
specification are herein incorporated by reference in their entirety to the same extent as if each
individual publication was specifically and individually indicated to be incorporated by
10 reference.

FIELD OF THE INVENTION

[0004] Described herein are systems and methods for treating tissue, such as neuronal tissue
and particularly brain tissue using Transcranial Magnetic Stimulation (TMS) to modulate the
susceptibility of the target tissue to pharmaceutical and/or radiation treatment.

BACKGROUND OF THE INVENTION

[0005] Treatment of disease, pain and medical disorders using drugs and/or ionizing
radiation (e.g., pharmacotherapy) may be more effective and may have fewer or less severe side-
effects when that available of the drug/radiation treatment to a targeted tissue (for example a
tumor or other diseased area of the body) is enhanced and/or where availability of the
20 drug/radiation to non--targeted tissue is minimized. For example, radiation therapy and
stereotactic radio surgery may be made more effective and less damaging to non-targeted tissues
if targeted tissues such as tumors are radio sensitized prior to treatment, or when surrounding
non-targeted tissue are radio protected.

[0006] The availability of a pharmaceutical to a given tissue in the body is determined by
25 several factors including the concentration of the drug in the systemic circulation, plasma protein
binding, the solubility of the drug within that organ, histological/anatomical barriers, the size of
the tissue, and the blood flow or perfusion of that tissue. Specifically, the better perfused a
tissue, the more drug is brought to a tissue per unit time. (e.g., Brunto et al, Moskowitz et al).

[0007] The sensitivity of a given tissue in the body to the effects of ionizing radiation is
30 determined by several factors including the rate of cellular division, the state of differentiation of
the cells, the degree of nourishment to those cells including blood perfusion, and the metabolic
rate of that tissue (e.g., Rubin and Casarett). Better-nourished tumors are paradoxically more

radiosensitive than those that are marginally nourished, although such tissue may also be better capable of carrying out repair to radiation-injured tissue. Most importantly, the higher the metabolic rate of a tissue, the more radiosensitive it is (Ueno 1971, Kimeldorf et al 1950, Smith et al 1951, Blount et al 1949, Rubin et al 1968).

5 [0008] Magnetic stimulation is a known method by which the perfusion of and the metabolic rate of targeted tissue may be alternatively increased or decreased (Zheng et al, Li et al, George et al, Speer et al).

[0009] The methods and systems described herein apply targeted magnetic stimulation to change the perfusion and metabolic rate of tissue, thereby making selected tissue more
10 susceptible to the effects of a drug or ionizing radiation, and for making non-targeted tissue less susceptible to such effects.

[00010] References that my help provide context and background include, and may be referred to as indicated above include:

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15 metabolic rate.

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- [00025] Zheng H, Zhang L, Li L, Liu P, Gao J, Liu X, Zou J, Zhang Y, Liu J, Zhang Z, Li Z, Men W. High-frequency rTMS Treatment Increases Left Prefrontal Myo-Inositol in Young Patients with Treatment-Resistant Depression. Prog Neuropsychopharmacol Biol Psychiatry. 2010 Jun 23.

SUMMARY OF THE INVENTION

[00026] Described herein are methods for enhancing or inhibiting (or a combination of both) susceptibility of a tissue (and particularly brain tissue) to pharmacological (drug) and/or radiation treatment by applying magnetic stimulation to up-regulate or down-regulate activity of one or more target tissue regions.

[00027] As described herein, magnetic stimulation, including transcranial magnetic stimulation (TMS), is applied used to alter the blood flow and metabolic rate of a portion of the body. In one embodiment, the diseased portion of the body slated for radiation or pharmacotherapy is up-regulated such that blood perfusion and metabolic rate of that tissue are increased thereby sensitizing this area to the effects of radiation and of drugs. In another embodiment, non-diseased portions of the body are down-regulated such that blood perfusion and metabolic rate of that tissue are decreased, thereby helping to protect those portions of the body from the effects of radiation and of drugs. In another embodiment, tissue that has been damaged from the effects of radiation and/or drugs may be up-regulated such that increased blood perfusion and metabolism may help with the cellular and tissue repair process.

BRIEF DESCRIPTION OF THE DRAWINGS

[00028] FIG. 1 illustrates one example of treatment of a target tissue (in this example, brain tissue) using magnetic stimulation to alter the susceptibility of the tissue to treatment by a drug or radiotherapy.

DETAILED DESCRIPTION OF THE INVENTION

[00029] Included are systems and methods for modulating the susceptibility of one or more tissue regions to a pharmacological and/or radiation therapy. In general, a target tissue region may be made more susceptible to a pharmacological and/or radiation treatment by up-regulating the region through the application of magnetic energy. Similarly non-target tissue regions may be made less susceptible to a pharmacological and/or radiation therapy by down-regulating the region through the application of magnetic energy. The orientation and/or frequency of applied magnetic energy may result in selectively up-regulating and/or down regulating metabolic activity.

[00030] For example, transcranial magnetic stimulation (TMS) is known to modulate metabolic activity in targeted brain regions, which may be visualized using scanning techniques such as PET scans. There is a widespread belief that low-frequency stimulation of target brain regions causes down-regulation (e.g., inhibition) of the target brain regions, while up-regulation may be achieved using high-frequency (e.g., greater than 5 Hz) stimulation. Work in our lab has suggested that the orientation of the applied TMS may also contribute to determine if a region is up-regulated or down-regulated; in particular, preliminary studies suggest methods of achieving low-frequency TMS (e.g., less than 3 Hz) that results in up-regulation of target brain regions, particularly when the TMS coil(s) are oriented so that the induced current or the principle current at the apex of the TMS electromagnet is oriented transversely to the AP axis of a subject's head (e.g., the AP axis of the head, skull, brain, etc.).

[00031] In particular, described herein are methods of performing TMS at to up-regulate or down-regulate target regions (e.g., a target brain region) and thereby modulate the sensitivity of the target region to a therapy such as a pharmacological, immunological, or radiation therapy.

[00032] As used herein, low-frequency TMS may be used synonymously with slow rate or slow rTMS pulse rates, and may be between about 0.5Hz to about 3 Hz. This low-frequency or slow rate rTMS pulse rates may be contrasted to traditionally "fast" rTMS pulse rates (e.g., between about 5-50 Hz). Thus, in some variations, low-frequency TMS may be less than about 5 Hz. As mentioned, low-frequency TMS is widely believed to result in inhibition of the target region, while high-frequency TMS is thought to result in up-regulation of the target region.

[00033] FIG. 1 illustrates one example of a method and system for modulating the susceptibility of a brain region to a pharmacological, immunological or radiation therapy. In FIG. 1, a target region 110 of a brain 100 is up-regulated with magnetic stimulation to increase the radio sensitivity of the tissue. Non-target regions 111 may be down-regulated by the selective application of TMS. In this example, a magnetic coil 120 is used to apply a magnetic stimulation process 121, immediately before, during or shortly after application of a drug 130 (e.g., using a drug delivery process 131 such as injection, oral, transcutaneous, etc.) and/or radiation treatment using a radiation treatment device 140 and an appropriate radiation delivery process 141. Thus a disorder may be treated by the overlapping application of a treatment modality (e.g., pharmacological treatment) with a magnetic stimulation that modulates the activity.

[00034] In some variations, the targeted tissue region is modulated simultaneous with the application of drug/immune agent/radiation, so that the applied magnetic field up- or down-regulates activity of the region resulting in a change in the perfusion rate of the target tissue and therefore either inhibiting or enhancing the susceptibility of the target region.

[00035] In another example, non-target brain regions may be made less sensitive to treatment (e.g., drug/radiation treatment) by magnetic stimulation. For example, down regulation of a targeted area by magnetic stimulation may be used to decrease radio-sensitivity of tissue. In some variation a target brain region may be up-regulated to enhance susceptibility to treatment while at the same time adjacent non-target brain regions may be made less sensitive by down-regulation. For example, a plurality of TMS coils may be used at different orientations and frequencies of stimulation to up-regulate some brain regions and to down-regulate others.

[00036] In one variation, magnetic stimulation may be used to improve tissue recovery at non-target region. For example, up-regulation of targeted areas by magnetic stimulation may increase blood flow and metabolic rate, thereby speeding healing processes. This may be performed in conjunction with the application of one or more drugs, compounds, therapeutic substances or the like, which may further enhance healing.

[00037] In some variations, magnetic stimulation may be applied to body region to increase drug availability at the target regions by increasing blood perfusion of that region, as mentioned above. Up-regulation of targeted area may increase local drug availability, aiding in targeting of the drug uptake and/or effect. Magnetic stimulation of a targeted tissue region may also decrease the availability of the drug at non-target regions by decreasing perfusion in these non-target regions. Down-regulation of non-targeted areas may lower local drug availability.

[00038] Although the examples provided herein describe primarily the use of magnetic energy (e.g., magnetic stimulation) to increase or decrease the susceptibility of tissue to a treatment such

as drug, immuno-agent or radiation, any appropriate energy modality may be used. In particular, non-contact energy modalities may be used such as microwave, ultrasound, or the like. Further, the target tissue may be any appropriate tissue, and may not be limited to brain tissue or brain regions.

[00039] The various embodiments described above are provided by way of illustration only and should not be construed to limit the invention. Based on the above discussion and illustrations, those skilled in the art will readily recognize that various modifications and changes may be made to the present invention without strictly following the exemplary embodiments and applications illustrated and described herein. Such modifications and changes do not depart from the true spirit and scope of the present invention.

CLAIMS

What is claimed is:

- 5 1) A system for increasing the therapeutic effect of radiation upon targeted area of tissue comprising:
a radiation source for directing radiation toward a target; and
a magnetic field source configured to be steered so that the magnetic energy is
delivery toward the target;
whereby treatment with the magnetic field prior to radiation delivery sensitizes target
10 tissue to the effects of radiation.
- 2) The system of claim 1, wherein the magnetic field source comprises a Transcranial
Magnetic Stimulation electromagnet.
- 15 3) The system of claim 1, wherein the magnetic field source comprises a plurality of
Transcranial Magnetic Stimulation electromagnets configured to target a deep brain
region.
- 4) The system of claim 1, wherein the system further comprises a controller configured to
20 coordinate timing of the delivery of the magnetic field and the radiation.
- 5) A system for decreasing the effect of radiation upon non-targeted tissue comprising:
a radiation source for steering radiation selectively towards targeted tissue regions
while avoiding non-target tissue regions; and
25 a magnetic field source configured to be steered toward non-targeted regions;
whereby treatment with the magnetic field prior to radiation delivery de-sensitizes
said non- target tissue to the effects of radiation.
- 6) A system for optimizing therapeutic radiation treatment comprising:
30 a radiation source configured to direct radiation toward a tissue target; and
a magnetic field source configured to be steered so that the magnetic energy is
delivered to target or non-target tissue regions;

whereby treatment with the magnetic field after radiation delivery improves tissue recovery of electrically active cells following radiation exposure.

5 7) A method of increasing the effect of a drug upon targeted area of tissue, the method comprising:

delivering a drug that reaches a target body tissue via blood vessels to a patient;
steering a magnetic field source so that the magnetic energy is delivered to the
patient's target tissue; and

10 applying magnetic field energy to increase the perfusion of targeted tissues, whereby availability of drug to targeted tissues is increased.

8) A system for decreasing the effect of a drug upon non-targeted tissue comprising:
a drug which reaches body tissue via blood vessels:

15 delivering a drug that reaches a target body tissue via blood vessels to a patient;
steering a magnetic field source so that the magnetic energy is delivered to the
patient's non-target tissue; and

applying magnetic field energy to decrease the perfusion of the non-target tissue,
whereby availability of drug to targeted tissues is reduced.

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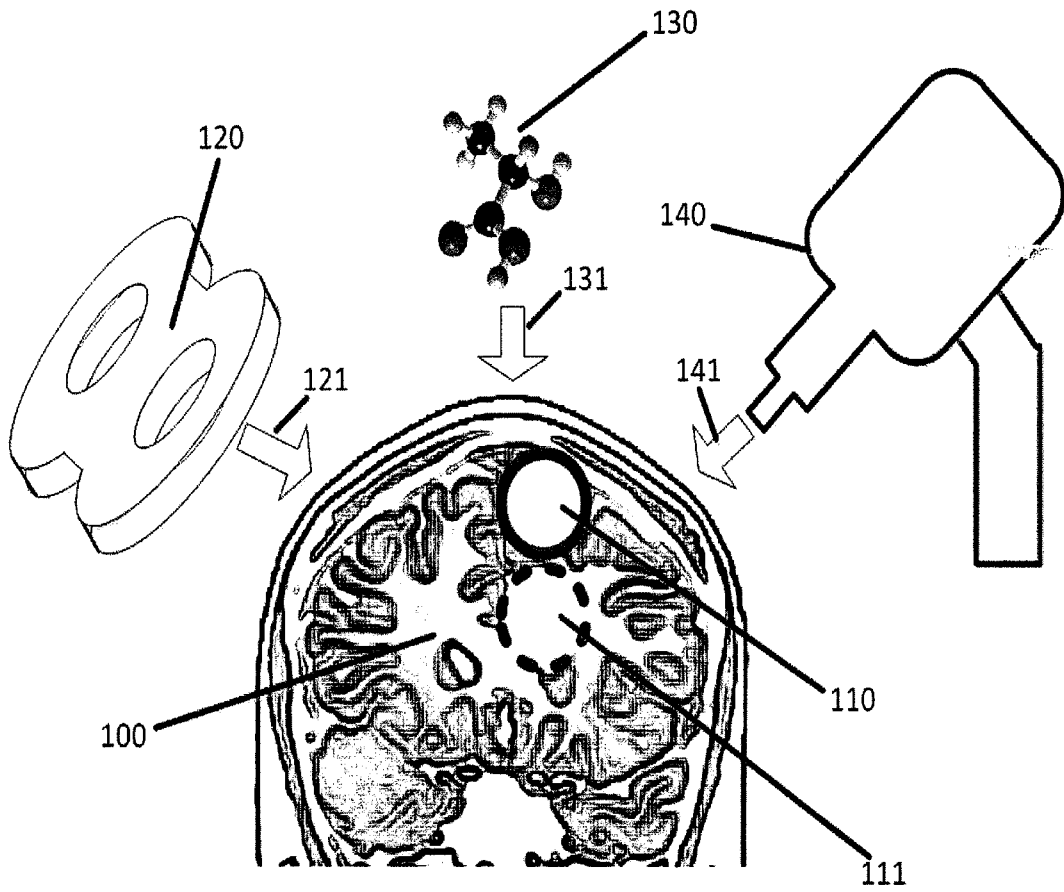


FIGURE 1