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INT CL **A61N**
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(54) Title of the Invention: **Supplying a neurostimulation signal**
Abstract Title: **Transcranial alternating current neurostimulation using first and second applied signals to create a third interference signal**

(57) Apparatus for suppling a transcranial alternating current neurostimulation signal to a human brain comprises a first signal generating device 531 which supplies a first signal 301 (Figure 3) at a first frequency to said human brain, in combination with a second signal generating device 532 which supplies a second signal 302 (Figure 3) at a second frequency. A third signal 313 at a third frequency is created due to interference between the first signal and the second signal. The apparatus may further comprise a receiver 501 for receiving output signals from said human brain, comprising a low-pass filter 543 and an amplifier 544, such that the received signal can be separated from the first and second signals by the low-pass filter. The received signal may be received by one or more electroencephalogram (EEG) electrodes.

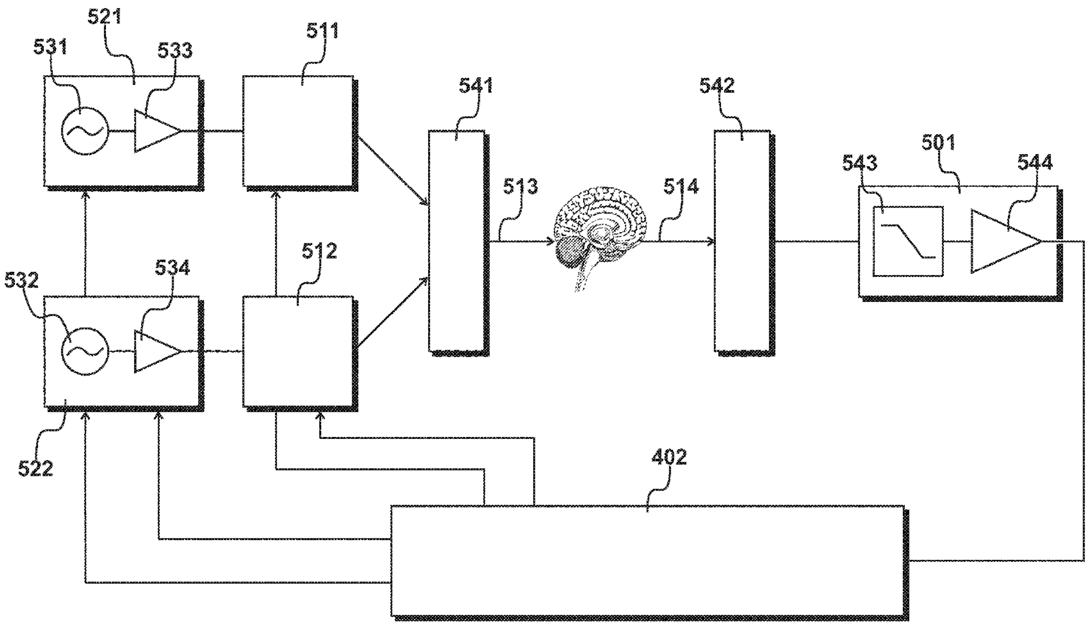

Fig. 5

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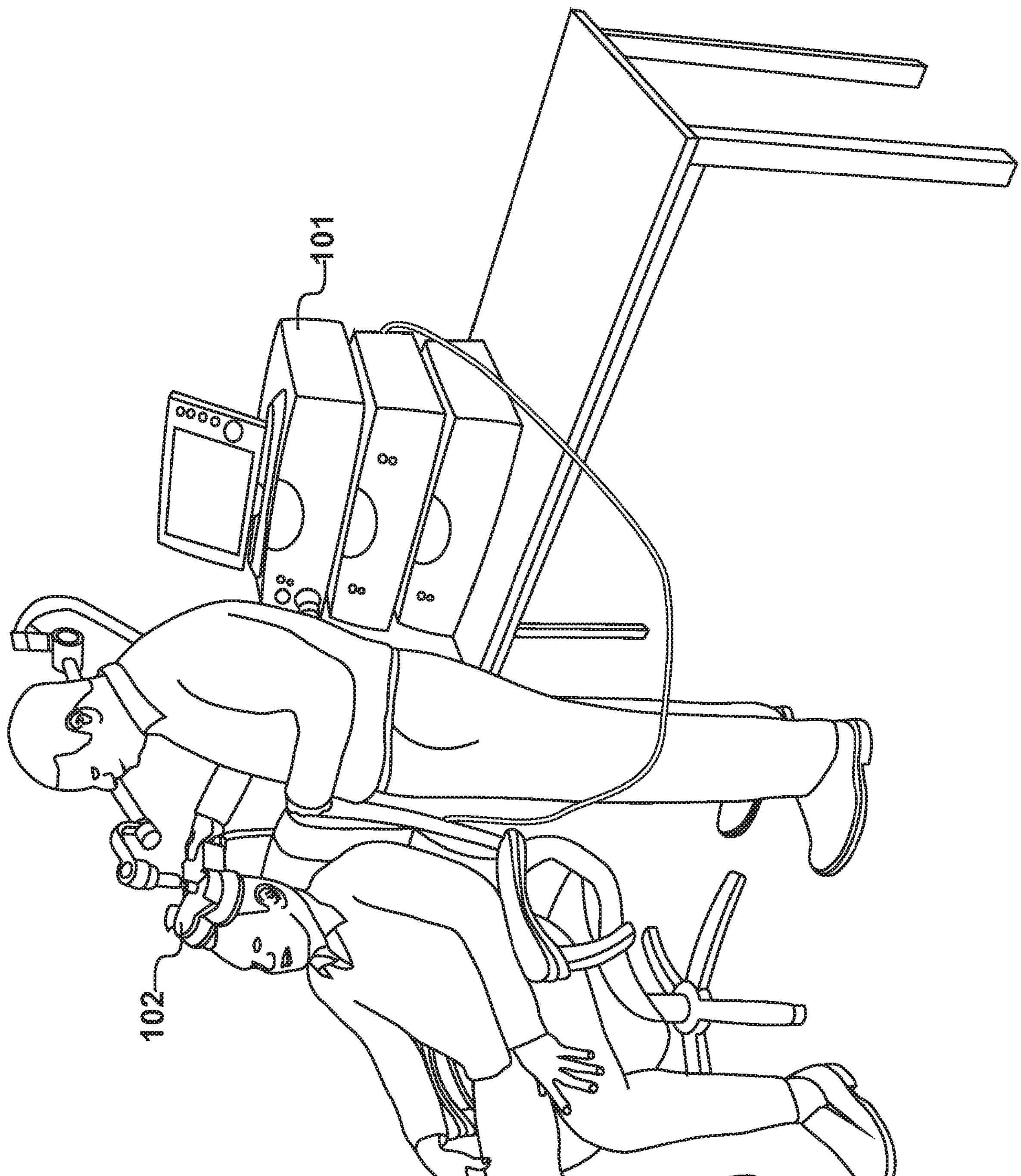

Fig. 1

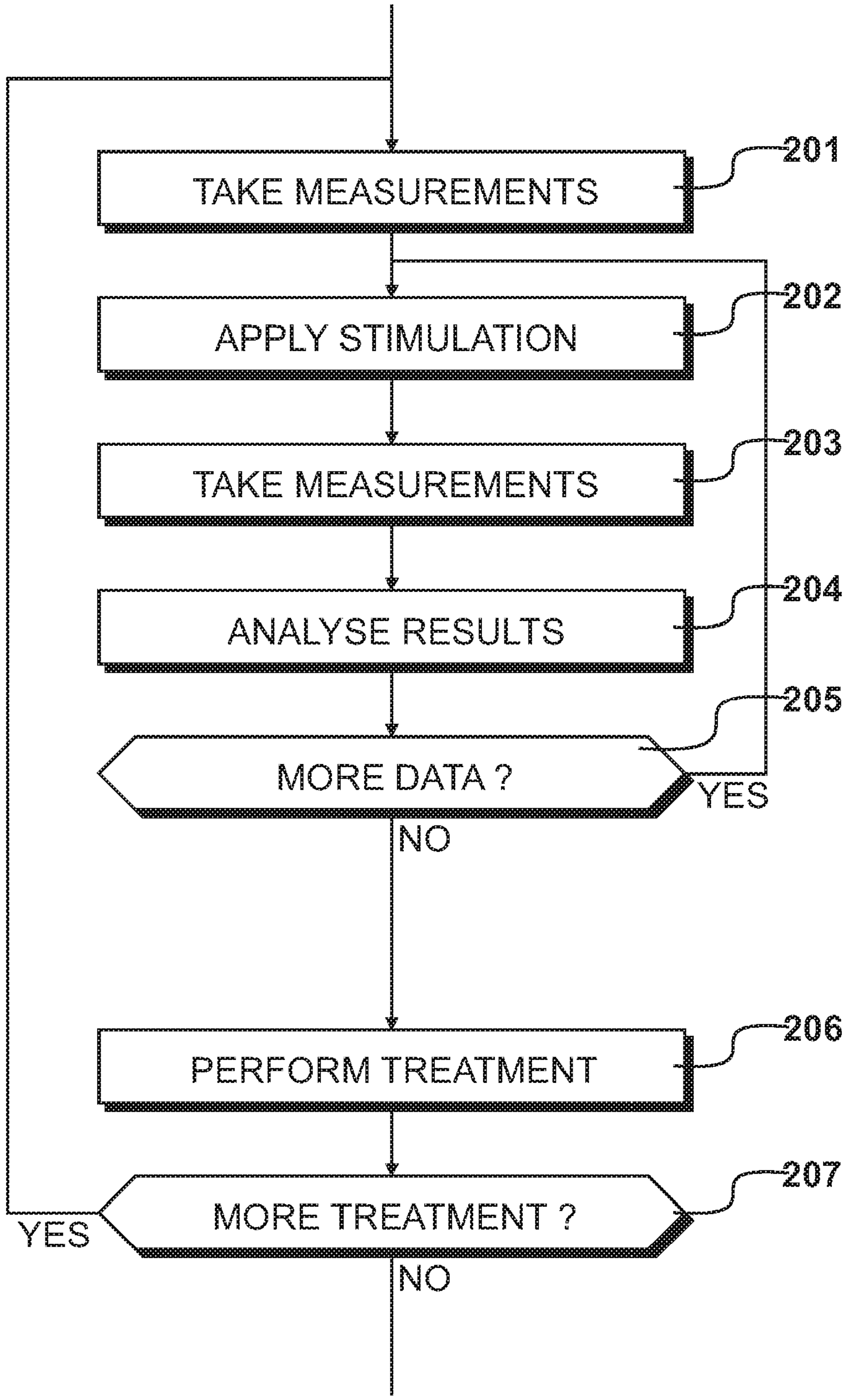
TAKE MEASUREMENTS
201
APPLY STIMULATION
202
TAKE MEASUREMENTS
203
ANALYSE RESULTS
204
MORE DATA ?
205
YES
NO
PERFORM TREATMENT
206
MORE TREATMENT ?
207
YES
NO

Fig. 2

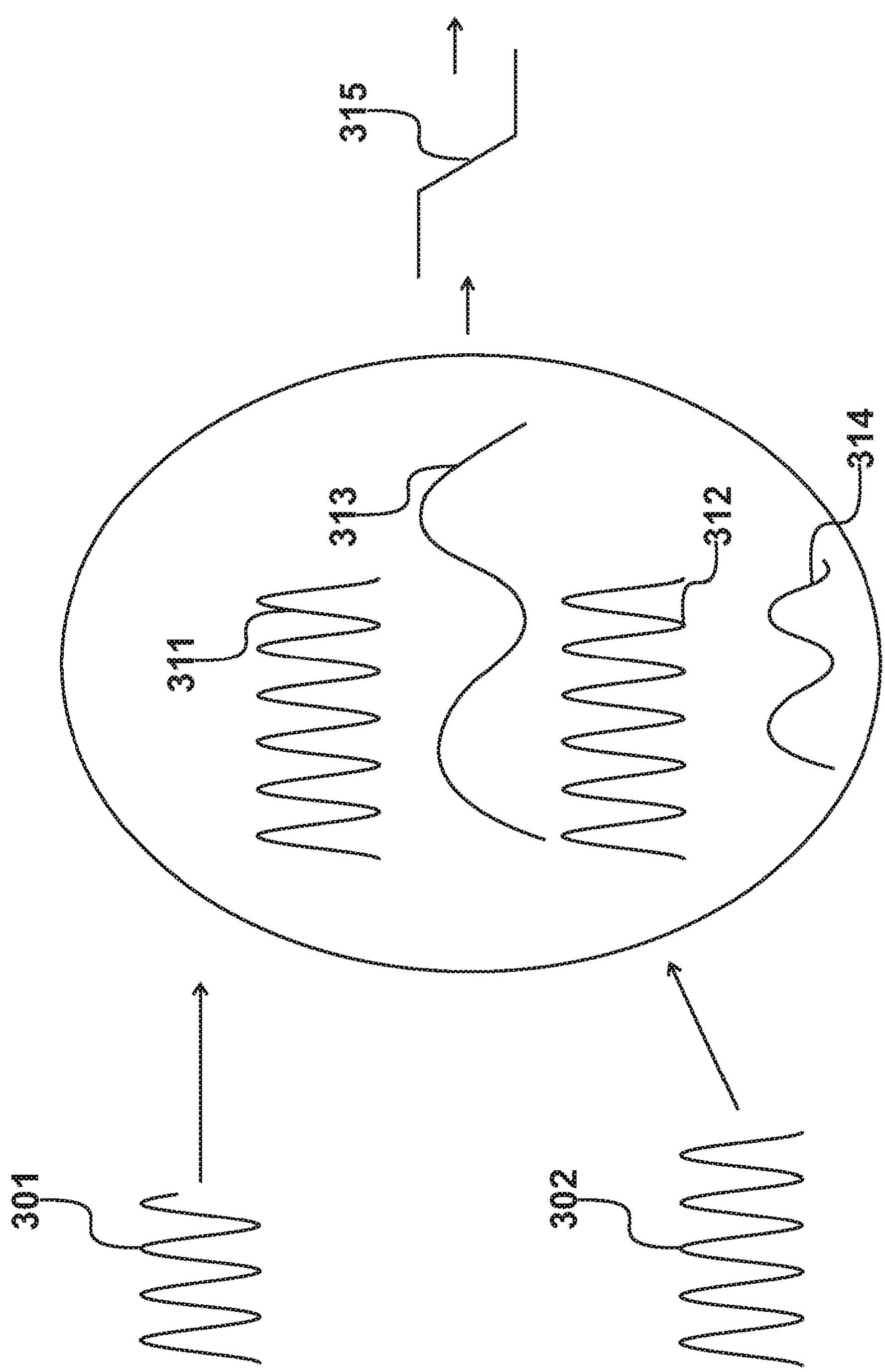

Fig. 3

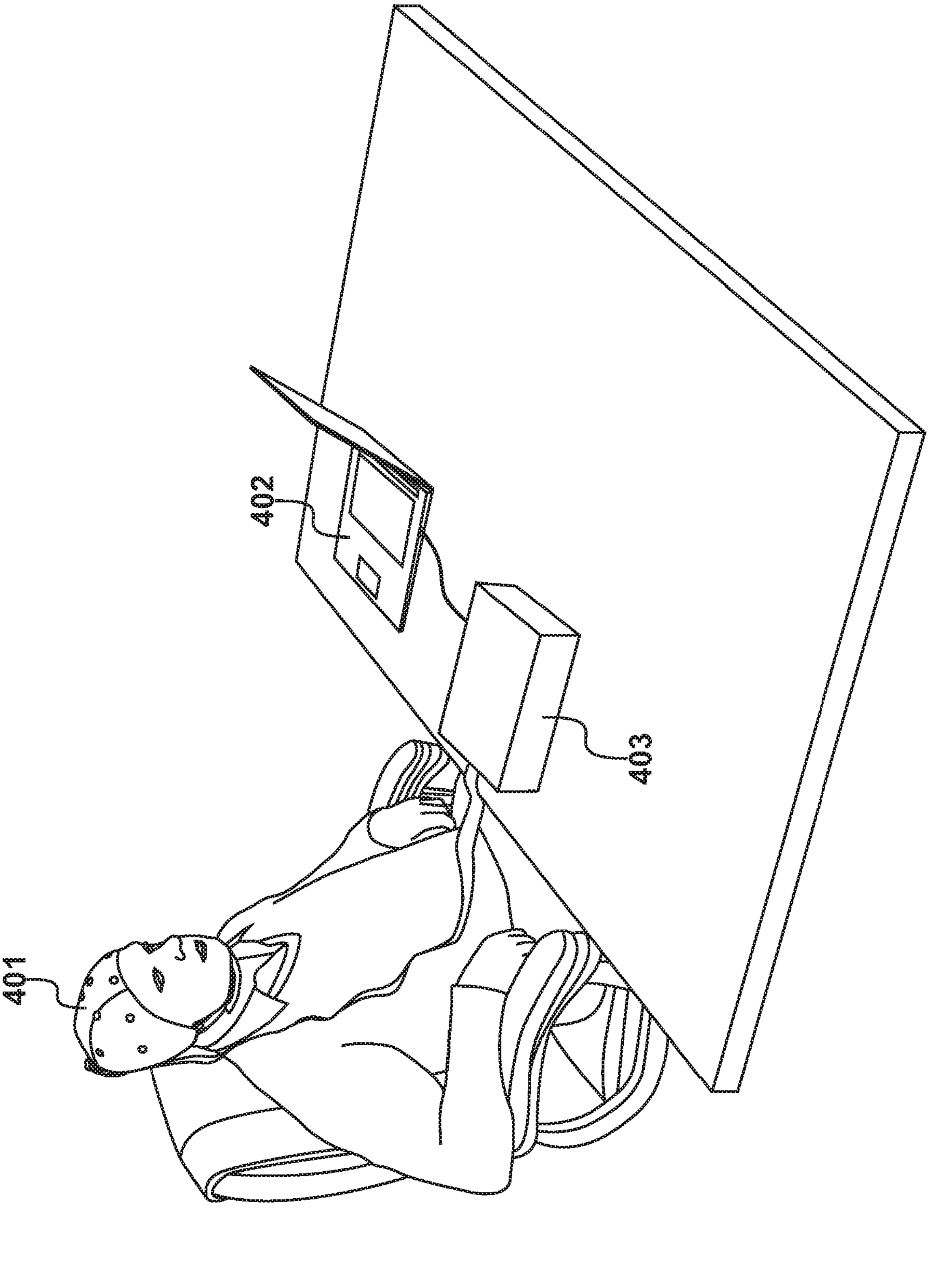

Fig. 4

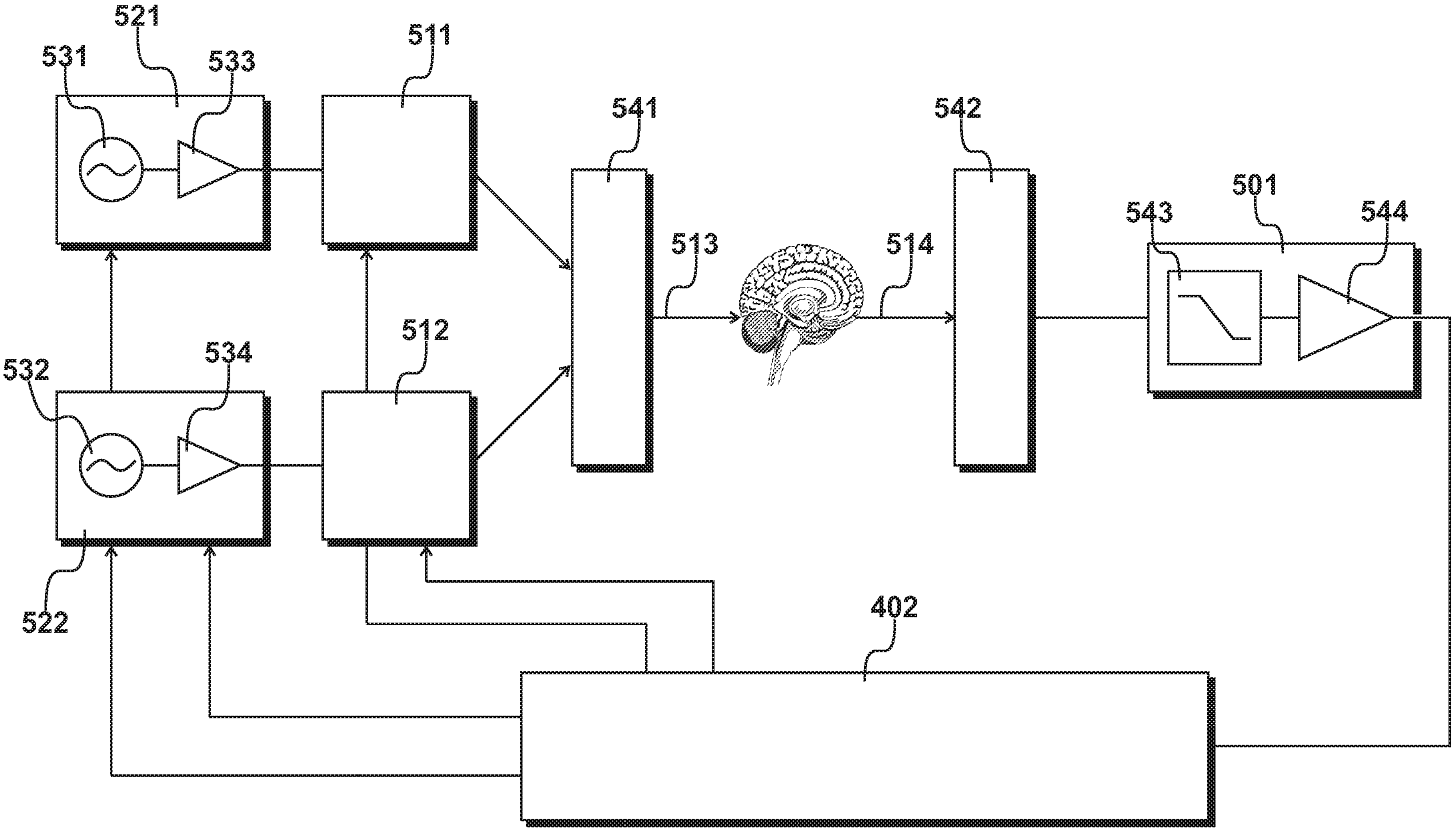

Fig. 5

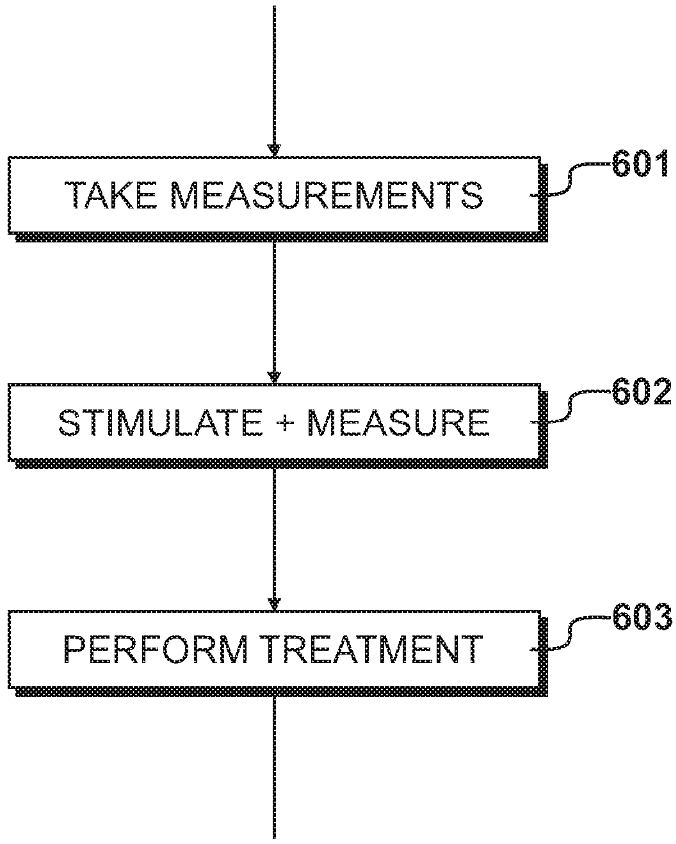
TAKE MEASUREMENTS
601
STIMULATE + MEASURE
602
PERFORM TREATMENT
603

Fig. 6

Supplying a Neurostimulation Signal

The present invention relates to an apparatus for supplying a transcranial alternating current neurostimulation signal to the human brain.

The present invention also relates to a method of supplying a transcranial alternating current neurostimulation signal to a human brain.

Living brains exhibit measurable electrical activity, that can be recorded in the form of an electroencephalogram (EEG). Sometimes brains show abnormal patterns of EEG activity which relate to conditions such as depression, ADHD or sleep disorders. Clinicians are known to supply tACS neurostimulation signals, via scalp electrodes, to the human brain in attempt to correct EEG abnormalities.

It is not currently possible to see the immediate effect that a particular tACS neurostimulation has on an EEG and thereby quickly determine if that neurostimulation is suitable or not for a participant's brain. Under normal conditions, attempting to measure EEG while tACS neurostimulation is being applied to the brain results in the EEG being completely drowned-out by the relative strength of the tACS signal. This is because the magnitude of the EEG is extremely small (10 to 100 micro volts) compared to the magnitude of typical tACS signals (10 to 30 volts). A problem therefore exists in terms of providing an appropriate neurostimulation signal while at the same time ensuring that this signal does not totally mask any output signals of scientific or clinical interest. For this reason, clinicians presently never attempt to view or record EEG while tACS neurostimulation is being given.

According to a first aspect of the present invention, there is provided an apparatus for supplying a transcranial alternating current neurostimulation signal to a human brain, comprising: a first signal generating device configured to supply a first signal at a first frequency to said human brain; and a second signal generating device configured to supply a second signal at a second frequency to said human brain, wherein: a third signal at a third frequency is created due to interference between said first signal and said second signal.

An embodiment further comprises a receiver for receiving output signals from said human brain in response to the neurostimulation. The receiver may include a low pass filter and an amplifier, such that the first signal and the second signal are applied to the scalp and EEG signals are supplied to the amplifier but the first signal and the second signal are blocked by the low pass filter. The third signal may be supplied to the amplifier via one or more EEG scalp electrodes.

According to a second aspect of the present invention, there is provided a method of supplying a transcranial alternating current neurostimulation signal to a human brain, comprising the steps of: supplying a first signal at a first frequency to said human brain; and supplying a second signal at a second frequency to said human brain, wherein: a third signal at a third frequency is created due to interference between said first signal and said second signal.

In an embodiment, the method further comprises the step of receiving output signals from the human brain in response to the neurostimulation. The receiver may include a low pass filter and an amplifier, such that the first signal and the second signal are applied to the scalp and EEG signals are supplied to the amplifier but said first signal and said second signal are blocked by said low pass filter. The third signal may be supplied to the amplifier via one or more EEG scalp electrodes.

Embodiments of the invention will be described, by way of example only. The detailed embodiments describe the best mode known to the inventor and provide support for the invention as claimed. However, they are only exemplary and should not be used to interpret or limit the scope of the claims. Their purpose is to provide a teaching to those skilled in the art. Components and processes distinguished by ordinal phrases such as “first” and “second” do not necessarily define an order or ranking of any sort. In the drawings:

Figure 1 shows an apparatus for applying transcranial magnetic stimulation;

Figure 2 illustrates a known approach for deploying the apparatus described with reference to *Figure 1*;

Figure 3 illustrates the generation of a third signal in response to receiving two input signals;

Figure 4 illustrates that the deployment of a thirty-eight-channel electro cap;

Figure 5 shows a schematic representation of apparatus embodying the present invention; and

Figure 6 illustrates a method for deploying the apparatus identified in Figure 5.

Figure 1

An apparatus **101** is shown in Figure 1 applying transcranial magnetic stimulation, which involves stimulating the brain of a patient with electromagnetic pulses at a frequency of around ten Hz. An electromagnet **102** is often positioned at the top front side of a patient's head and evidence shows that this can be a safe and effective treatment for depression.

Recent experiments have also shown that benefits can be gained from encouraging better communication between regions of the brain – often identified as Brodmann areas, following the work of Korbinian Brodmann. However, for this to be effective, it is necessary to identify appropriate positioning and stimulation frequencies. Thus, after identifying the frequencies that have been found to have an effect, these can be deployed during treatment.

Figure 2

A known approach to deploying the apparatus described with reference to *Figure 1* is illustrated in *Figure 2*. The treatment step is identified at step **206**. Prior to this, investigations are performed to determine how the treatment performed at step **206** may be optimised.

At step **201**, initial measurements are taken by means of an EEG in an attempt to identify abnormal patterns of activity.

At step **202**, stimulation is applied using a neuro stimulator, typically applying potentials of between ten to thirty volts. It has been recognised that it would be advantageous to take measurements while the stimulation is being applied. However, the magnitude of a typical EEG signal ranges from ten to one-hundred micro volts and as such is totally masked by the stimulation signal. Thus, the best that can be done is to take further measurements at step **203** after the application of stimulation, analyse these results at step **204** and ask a question at step **205** as to whether more data is required. Thus, this process can be repeated until the appropriate data has been received, thereby allowing the treatment to be performed at step **206**, followed by a question being asked at step **207** as to whether more treatment is required.

In response to the question asked at step **207** being answered in the affirmative, the whole process is repeated again, starting at step **201**.

It has been recognised that a way of improving the efficiency of the TMS procedure, described with reference to *Figure 1*, is to tune the stimulation frequency to match the natural resonant frequency of the client's brain.

Figure 3

Beats are well known in the field of acoustics and are generated when two sounds are created that have slightly different frequencies. The result is perceived as a periodic variation in volume and the beat rate is determined by the difference between the respective frequencies of the generated sounds.

The inventor has realised that a similar approach may be adopted for brain neurostimulation. The literature shows that tACS neurostimulations can have a significant beneficial effect upon a human electroencephalogram (EEG), which can be used for treating a range of neurological and physiological conditions. However, with current systems, it is difficult to determine the immediate effectiveness. In particular, it is very difficult to determine exactly how a given brain responds to a given neurostimulation while the neurostimulation is ongoing.

Potentials measured at the scalp are typically in the range of twenty to one-hundred micro volts, whereas the neurostimulation is typically given at ten to thirty volts. Thus, it is extremely difficult to see brain EEG signals, given that these signals are completely swamped by the size of the stimulating input signals.

The inventor has appreciated that, instead of using two sound sources, it is possible for the brain to be stimulated using two tACS frequencies, whose frequencies of tACS neurostimulation are far outside of the range of the EEG amplifier, which typically has a bandwidth of zero to one-hundred and twenty-eight Hz.

Known EEG amplifiers are provided with anti-aliasing filters to remove signals outside of the designated frequency range of operation. Essentially, they are provided with low-pass filters. Thus, by providing a composite interference neurostimulation signal that is far outside the frequency range of these amplifiers, it is possible to deploy frequencies of substantially higher range, typically 1700Hz to 1800Hz for example. With a neurostimulation signal being optimally adjusted, the original EEG signal can be seen, overlaid by the neurostimulation signal, emanating from the brain at the required EEG site.

In an example, a neurostimulation frequency of four Hz is required. To achieve this, it is possible to set a first tACS source to 1700Hz and a second tACS source to 1704Hz. Electrodes are attached to the scalp in the conventional way, selectively receiving the first signal at the first frequency or the second signal at the second frequency. The mix of the two signals induces a four Hz wave in the brain, which appears as if a four Hz signal had been deployed.

Calibration is required to ensure that the EEG signal remains clearly visible, while at the same time achieving the requisite level of neurostimulation. If the input signal strength is too high, the EEG is completely lost by the neurostimulation signal but if too low, the neurostimulation signal has no visible effect upon the recorded EEG output signals. In an embodiment, it is possible to achieve calibration by the use of a genetic algorithm, with the aim of deploying the minimal amount of neurostimulation in order to obtain the desired effect.

In the example shown in *Figure 3*, a first signal **301** has a frequency of eight-hundred-and-fifty-two Hz and a second signal **302** has a frequency of eight-hundred-and-ninety-two Hz. These applied signals propagate through the brain, as illustrated at **311** for the first signal and **312** for the second signal.

However, the two applied sine waves interfere to produce a third sine wave **313** having a frequency that is the difference between the frequency of the first signal **311** and the frequency of the second signal **312**. In this example, the third signal **313** has a frequency of forty Hz.

The purpose of the third signal **313** is to stimulate the generation of electrical activity within the brain. For the purposes of this example, it is assumed that a fourth signal **314** is produced within the brain as a result of the stimulation created by the third signal **313**.

As described with reference to *Figure 4*, output signals from the brain are monitored while stimulation is being applied. Output signals are supplied to amplification and monitoring equipment via a low-pass filter **315**. As a result of this, the first signal **311** and the second signal **312** cannot pass through the filter **315**, given that their frequency is too high. Consequently, on the output side of filter **315**, the fourth stimulated signal **314** is seen.

Figure 4

In an embodiment, a thirty-eight-channel electro cap **401** is deployed upon a subject, with nineteen of the available channels being used for neurostimulation and the other nineteen channels being arranged to provide an input to a Neurofield Q20 nineteen-channel EEG amplifier; following the international 10/20 standard. In an embodiment, each of the nineteen channels used for neurostimulation are adjacent to each of the standard nineteen channels being routed to the amplifier.

In an embodiment, a genetic algorithm runs on a personal computer **402** and initiates the neurostimulation signals from tACS neurostimulation units **403**, from which they are routed to electrodes on the EEG cap, possibly via two digitally controlled 16x16 analogue switches. In an embodiment, the control program running on a separate computer system, such as a Raspberry Pi computer, controls the configuration settings and routings of the switches under the control of the genetic algorithm running on the PC. In this way, the analogue switch devices can route any one of its tACS neurostimulation units to any one, many or all of the nineteen neurostimulation channels on the thirty-eight channel EEG cap.

Appropriately programmed oscillators produce twelve-volt signals in the 1700Hz range which are filtered by the anti-aliasing filters of the amplifier. The Q20 amplifier is configured to record signals in a frequency range of zero to one-hundred-and-twenty-eight Hz, with a typical amplitude range of zero to one-hundred microvolts and an EEG resolution of 0.02 microvolts.

The binaural interface pattern between the two alternating current signals, in the range of zero to one-hundred-and-twenty-eight Hz, induces a signal in the brain which may also be seen in real time across one, some or all of the nineteen EEG channels; without the EEG signal being swamped by the noise of the neurostimulation signal. Thus, by adopting this approach, both the EEG and the induced neurostimulation signal can be seen, provided that the amplitude of the neurostimulation signal is adjusted to be just visible at the target electrodes.

The objective of the genetic procedure is to find a neurostimulation location or locations, frequencies and intensities that cause the EEG to change in a predetermined way.

In an embodiment, the genetic procedure starts with a set of ten randomly chosen EEG sites / neurostimulation frequencies / neurostimulation currents. The goal of the genetic procedure is to find a neurostimulation pattern which results in a required change in EEG. Each of these neurostimulations is evaluated and scored. Each neurostimulation is applied to its target site, which may be a single site, many sites or all possible neurostimulation sites and the EEG is recorded as a neurostimulation is applied.

The neurostimulation is automatically calibrated, such that the neurostimulation signal is just visible on at least one of the recorded EEG channels. The neurostimulation that produces the biggest change in the required EEG is carried forward unchanged to the next generation; a process sometimes identified as elitism by those skilled in the art. The remaining nine members of the subsequent generation are created by making random changes to the best neurostimulation from the previous generation. The procedure then continues until there is no significant improvement towards the required change.

Thus, by adopting the approach of this embodiment, it is not necessary to make any assumptions about what configuration of stimulation frequency, intensity and site is likely to work. In an embodiment, the procedure is allowed to find an optimal neurostimulation to create the desired effect.

A possible approach to deploying the apparatus shown in *Figure 4* is to take an initial EEG recording for ten minutes with the subjects' eyes open and then perform this operation again with the subjects' eyes closed. With the eyes closed, the visual cortex starts producing alpha waves. If these are absent, it is likely to indicate that there is some kind of problem present. Thus, this approach allows the brain to be considered in two different states.

The approach then continues by taking a subsequent recording for about thirty minutes during which an electrode is attached to the front of the head with a similar electrode being attached to the back of the head. A range of signals are then applied having frequencies ranging from one Hz to forty Hz. These are played at random, so that the brain does not habituate to an ascending or descending pattern.

While the stimulation is being played into the brain, measurements are again taken. As described above, previously it was not possible to record data while stimulation was taking place because the EEG output signals in the range of twenty to fifty micro volts and the stimulation signal is in the range of ten to fifty volts.

Figure 5

As described with reference to *Figure 4*, the subject wears a thirty-eight channel EEG cap with nineteen of the channels being used for stimulation and the remaining nineteen channels providing an output to a Q20 EEG amplifier **501**.

A first 16×16 analogue switch **511** along with a second similar analogue switch **512** route alternating stimulation signals to one or more of the nineteen stimulation sites on the thirty-eight channel EEG cap under the control of the computer **402**. The nineteen input channels being identified at **513** in *Figure 5*, with the nineteen output channels identified at **514**.

A first Z3 tDCS/tACS unit **521** is provided with a similar second unit **522**; supplying output signals to the first analogue switch **511** and to the second analogue switch **512** respectively.

The first unit **521** includes a first oscillator **531**, with the second unit **522** including a second oscillator **532**. The output from the first oscillator **531** is supplied to the analogue switch **511** via an amplifier **533**. Similarly, the output from the second oscillator **532** is supplied to the second switch **512** via a second amplifier **534**.

Outputs from the analogue switches **511** and **512** are supplied to the input lines **513** via a first Dsub 25 breakout box **541**, with a second similar breakout box **542** supplying signals on lines **514** to the EEG amplifier **501**.

As shown in *Figure 5*, the signal generating units **521** and **522** along with the analogue switches **511** and **512** are controlled by the computer **502**. The computer **402** also receives output signals from the EEG amplifier **501**.

The EEG amplifier **501** includes, usually as standard, a low-pass anti-aliasing filter **543** and an output amplifier **544**. In this way, the twelve-volt signals in the 1700 Hz range produced by units **521** and **522** are blocked by the low-pass anti-aliasing filter **543**. The EEG amplifier is designed to record signals in the frequency range of zero to sixty Hz, with an amplitude range of plus or minus one-hundred milli-volts and an EEG resolution of 0.02 microvolts.

Thus, when deployed, a combination of frequencies is played into the brain that are outside of the bandwidth of the EEG amplifier **501**. This approach makes use of the amplifier's anti-aliasing filter to cut out frequencies above the desired range and as a consequence of this, the amplifier does not see the stimulation frequencies.

The interference pattern between the two stimulation signals induces a signal in the brain which can be seen in real time across some or all of the nineteen EEG output channels, without the EEG signal being swamped by the amplitude of the stimulation signal. The stimulation units produce a twelve-volt signal and the brain produces a signal in the range of fifty micro volts. Thus, the level of the stimulation signal is substantially greater than the output signal but by adopting this technique, both the EEG and the induced stimulation signal can be clearly seen.

The two high frequencies have a difference between them, therefore the brain experiences frequency differences and follows this stimulation frequency. It is therefore possible to see how the brain responds to specific stimulation frequencies in real time.

Output data received by the computer **402** may be processed locally or transferred for a more in-depth analysis. In an embodiment, commercial software sold under the trademark 'LORETTA' may analyse the data by adopting a three shell spherical head model registered to a standardised stereotactic space. This uses the signals received from the surface of the brain to deduce what is happening deep inside the brain.

In an embodiment, the first oscillator **531** is fixed to produce an alternating signal at eight-hundred-and-fifty-two Hz. The frequency of signals produced by the second oscillator **532** is variable, possibly ranging between eight-hundred-and-fifty-two Hz and eight-hundred-and-ninety-two Hz, to give an interference range of between zero to forty Hz. As previously described, these frequencies are applied to the brain at intervals for a fixed period of time in a random order.

Figure 6

By the deployment of aspects of the invention described herein, it is possible to move towards a more simplified working model, compared to that described with reference to *Figure 2*. At step **601** initial measurements are taken as described with reference to *Figure 4*. At step **602** stimulation and measurement is performed, as described with reference to *Figure 5*. Experiments have shown that by being in a position to stimulate and measure at the same time, the usefulness and accuracy of the output data received is substantially enhanced. Thus, it should be possible to move on to performing treatment at step **603** as described with reference to *Figure 1*.

This approach is achieved by performing a method of supplying a transcranial alternating current neurostimulation signal to the human brain by supplying a first signal at a first frequency to said human brain and supplying a second signal at a second frequency to the human brain. A third signal is created at a third frequency due to interference between the first signal and the second signal.

CLAIMS

1. An apparatus for supplying a transcranial alternating current neurostimulation signal to a human brain, comprising:

a first signal generating device configured to supply a first signal at a first frequency to said human brain; and

a second signal generating device configured to supply a second signal at a second frequency to said human brain, wherein:

a third signal at a third frequency is created due to interference between said first signal and said second signal.

2. The apparatus of claim **1**, further comprising a receiver for receiving output signals from said human brain in response to said neurostimulation.

3. The apparatus of claim **2**, wherein said receiver includes a low pass filter and an amplifier, such that said first signal and said second signal are applied to the scalp and EEG signals are supplied to said amplifier but said first signal and said second signal are blocked by said low pass filter.

4. The apparatus of claim **3**, wherein said third signal is supplied to said amplifier via one or more EEG scalp electrodes.

5. A method of supplying a transcranial alternating current neurostimulation signal to a human brain, comprising the steps of:

supplying a first signal at a first frequency to said human brain; and

supplying a second signal at a second frequency to said human brain, wherein:

a third signal at a third frequency is created due to interference between said first signal and said second signal.

6. The method of claim **5**, further comprising the step of receiving output signals from said human brain in response to said neurostimulation.

7. The method of claim **6**, wherein said receiver includes a low pass filter and an amplifier, such that said first signal and said second signal are applied to the scalp and EEG signals are supplied to said amplifier but said first signal and said second signal are blocked by said low pass filter.

8. The method of claim **7**, wherein said third signal is supplied to said amplifier via one or more EEG scalp electrodes.

Intellectual Property Office

Application No:	GB2206497.6	**Examiner:**	Mr Henry You
Claims searched:	1-4	**Date of search:**	20 September 2022

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
X	1-4	US 3951134 A (MALECH), see column 3, line 61 - column 4, line 49
X	1	WO 2016/057855 A1 (MIT), see paragraph 49
X	1	WO 2021/044168 A1 (IMPERIAL COLLEGE INNOVATIONS), see Figure 1 and page 12
X	1	US 2019/366087 A1 (FEINSTEIN), see Figure 1 and paragraphs 22 and 43
X	1	WO 2013/192582 A1 (NEUROTEK INC), see paragraphs 132-133
X	1	WO 2004/047911 A2 (INTERNATIONAL REHABILITATIVE SCIENCES), see Figure 2 and page 3

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC^{X} :

Worldwide search of patent documents classified in the following areas of the IPC

A61N

The following online and other databases have been used in the preparation of this search report

WPI, EPODOC

Intellectual
Property
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International Classification:

Subclass	Subgroup	Valid From
A61N	0001/32	01/01/2006
A61N	0001/36	01/01/2006