(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 267 703 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
17.11.2010 Bulletin 2010/46

(21) Application number: **01916739.4**

(22) Date of filing: **27.03.2001**

(51) Int Cl.:
A61B 3/00 *(2006.01)* ***A61B 5/00*** *(2006.01)*
A61B 5/0484 *(2006.01)*

(86) International application number:
PCT/AU2001/000343

(87) International publication number:
WO 2001/072211 (04.10.2001 Gazette 2001/40)

(54) **METHOD AND APPARATUS FOR ASSESSING NEURAL FUNCTION BY SPARSE STIMULI**

VERFAHREN UND GERÄT ZUR BEURTEILUNG NEUTRALER FUNKTIONEN DURCH SELTENE STIMULI

METHODE ET APPAREIL DESTINES A EVALUER LA FONCTION NEURONALE PAR STIMULI EPARS

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR

(30) Priority: **27.03.2000 AU PQ646500**

(43) Date of publication of application:
02.01.2003 Bulletin 2003/01

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US-A- 4 832 480

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Description

FIELD OF THE INVENTION

[0001] THIS INVENTION relates generally to assessment of neural function. More particularly, the present invention is concerned with a method and apparatus for assessment of neural function by temporally sparse stimuli with particular application to diseases affecting the sensory nervous system such as glaucoma, or diseases affecting nerve conduction such as multiple sclerosis.

BACKGROUND OF THE INVENTION

[0002] A conventional way to measure nervous system function is to record an evoked potential (EP) in response to a stimulus which is often presented repeatedly. The EP is a voltage representing the summed electrical activity of large number of neurones that reside near the recording electrodes. More recently, measurement of stimulus evoked responses (SERs) such as changes in magnetic fields or optical signals generated by neural activity have come into use. Another response generated by the nervous system providing possible utility is the pupillary response. Similarly the electroculogram, or eye movements measured in other ways, could be used. Such non-invasive measurement is desirable in the clinical setting and so neural activity is typically recorded from or through the skin in what might be described as surface recording. For example, evoked electrical potentials reflecting brain activity are easily recorded from electrodes placed upon the scalp. Magnetic and infrared signals related to neural activity can be similarly recorded through the skin. A potential drawback of surface measurements, or eye movements, or the pupillary response is that, however they are measured, these evoked responses typically represent the summed activity of many neurones in response to the stimulus.

[0003] Diseases affecting the nervous system may impact upon sections of the nervous system differentially. For example in the eye disease glaucoma separate parts of the retina are differentially affected causing localised reduction of visual performance in particular parts of the visual field. Like multiple sclerosis the damage caused by the disease is localised to small regions along the nerves and neural pathways within the brain. Thus, in such cases it would be useful to test neural function with multiple stimuli at the same time, each stimulus testing a different section of the nervous system, in what might be called Multi-stimulus Evoked Responses (MSERs). Measurement of MSERs to some extent minimises the difficulties of recording evoked responses. So, for example, stimuli presented to multiple parts of the visual field at the same time would in principle allow efficient mapping of the visual field even with a single recording sensor placed on or near the eye or scalp. Thus, the problems of recording evoked responses are reduced when responses to stimuli to multiple parts of the nervous system can be recorded.

[0004] While some MSER methods have been proposed, the emphasis in the design of the stimulus sequences used to date has been to reduce the computational burden in estimating the responses and/or to reduce the degree of correlation between the stimulus sequences. For example, Wiener, N ("Nonlinear problems in random theory", New York, Wiley, 1958) proposed the use of continuous Gaussian distributed white noise as a stimulus sequence that in principle could be used for MSERs. More recently Sutter, E (U.S. Patent Serial No. 4,846,567) proposed the use of special stimulus sequences called m-sequences where the stimulus sequence fluctuates between one of two levels in a strictly defined way. These two level m-sequences are a subset of a class of sequences that are said to be binary. These binary sequences vary between two about equally likely stimulus conditions and thus, unlike the stimuli proposed hereinafter, never contain a null condition and are not sparse in the sense presented herein. Neither of the stimuli of Wiener or Sutter is designed to optimise responses from any particular part of the nervous system. Stimuli that permit the measurement of MSERs but which are optimised for assessing clinically relevant parts of the nervous system would be potentially more useful.

[0005] Of particular interest in assessment of neural function may be those parts of the nervous system that dynamically adapt to prevailing stimulus conditions by using so called gain control mechanisms. These neural systems are interesting from the point of view of studying neural performance because these gain control systems are often complex and strictly controlled. Thus, neural dysfunction might be readily observed in neural systems exhibiting gain control mechanisms. At the same time appropriate design of stimulus sequences might permit neural systems with gain control systems to produce larger and or more reliable responses.

[0006] WO99/34727 describes a method of enhancing and extracting second-order nonlinear response components. Two modes of stimulation and analysis are performed for enhancement of local, lateral non-linear interactions in multi-area electroretinogram. One stimulus occurs at a predetermined time within each equal-sized interval and the other stimulus occurs pseudorandomly at the beginning of the intervals.

[0007] WO99/49776 describes the utility of computing interaction kernels (nonlinear weighting functions) that isolate the separate effects caused by the merger of two streams of information thus isolating response from the point of the merger within the brain.

SUMMARY OF THE INVENTION

[0008] The present invention arises in part from the discovery that a low probability of encountering a stimulus differing from a baseline or null stimulus condition in sparse stimulus sequences as defined hereinafter insures that gain control mechanisms within the nervous

system will increase the neural response magnitude and also bias the measured responses to those neurone populations having such gain controls. Sparse stimuli consist of temporal sequences of stimulus conditions presented against a baseline null stimulus condition, where the non-null stimulus condition, or conditions, are presented relatively infrequently. The consequently increased response amplitudes ensure more reliably recorded responses than are obtained with non-sparse stimuli. The inventors consider that biasing the response to those neural systems with gain controls will bias neural assessment to dynamic neural systems that are likely to become defective in disease.

[0009] The inventors have also discovered that even fairly short pseudorandom sparse stimulus sequences can be used to characterise the response of the nervous system by estimation of linear and non-linear weighting functions such as Wiener or Volterra kernels. Estimation of such kernels permits multiple stimulus sequences to be presented to the nervous system at the same time, and separate kernels to be estimated for each stimulus sequence. Simultaneous estimation of responses adds statistical power to the overall assessment process. It has also been surprisingly found that multiple stimuli such as, for example, ternary stimuli comprising a non-stimulus condition and two non-null stimulus conditions also permit separate and simultaneous estimates of kernels characterising responses to each of the non-null stimulus conditions within a ternary sequence. The inventors consider that such multiple stimuli, such as sparse ternary sequences consisting of infrequently presented bright and dark departures from a background null brightness level would be useful, for example, in testing for damage to those populations of visual neurones that respond separately to image points that are either darker or lighter than the average.

[0010] Thus, the prime objective of the present invention is the provision of a rapid reliable test for damage to the nervous system by measuring responses to multiple, simultaneously presented, stimuli, that appeal to gain control mechanisms of the nervous system, where such gain control mechanisms will enhance the responses to the stimuli and thus make the recorded responses more reliable. A preferred objective is to use stimuli that also permit isolation of responses from neurones that encode about half the sensory range as, for example, in the sets of visual neurones that encode information about parts of the visual field that are brighter or darker than average. Another objective of appealing to neural gain control mechanisms in the case of stimulation of the left and right sensory fields (e. g., to the left and right halves of the visual field) is to increase the symmetry of neural responses arising from the left and right sensory fields. All these objectives can be met by use of a particular class of stimuli termed sparse stimulus sequences.

[0011] Accordingly, there is a method for simultaneously assessing the functional status of component parts of the nervous system of a subject, said method comprising:

presenting to multiple component parts of the sensory nervous system of the subject stimulus sequences having different temporal modulation sequences of the appropriate stimulus modality for each stimulated part of the sensory nervous system, the stimuli having different sequences for each stimulated part;

temporally modulating the stimuli between a null stimulus condition and at least one non-null stimulus condition selected from the group consisting of an increment stimulus condition and a decrement stimulus condition, relative to the null stimulus condition, wherein the probability of encountering the null stimulus condition in the stimulus sequences is higher compared to the probability of encountering the at least one non-null stimulus condition, and wherein the temporally modulated stimuli permit estimation of linear and non-linear weighting functions characterising measured responses to each stimulus presented to each component part of the nervous system;

estimating some or all of the coefficients of the linear and non-linear weighting functions for each stimulus sequence from the measured responses to said stimuli, to isolate separate responses from the separately and simultaneously stimulated component parts of the nervous system; and

estimating separate coefficients for responses to said other stimulus conditions to permit isolation of separate responses from component parts of the nervous system that respond to distinct members of said other stimulus conditions;

characterised in that the at least one non-null condition occurs with an average frequency of between about 0.25 and about 6 per second and that the stimulus sequences comprise aperiodic or pseudorandom stimulus sequences..

[0012] The non-null stimulus conditions include stimulation of a sensory modality. In a preferred embodiment of this type, the stimulation is selected from the group consisting of tactile stimuli, auditory stimuli and visual stimuli or a combination thereof.

[0013] The auditory stimuli may comprise different pressure levels or different tones, The tactile stimuli include any suitable somatosensory stimuli, including different pressure levels and different frequencies of a stimulus pressed against the skin or other tissues. The visual stimuli may comprise images of different brightness, whether actual or illusory, different luminance or contrast levels or modulations, different colours or colour contrasts, different patterns, textural densities or types, different pattern orientations or direction of movement, different image sizes, i. e., any valid modulation of the visual nervous system.

[0014] In a preferred embodiment, the stimulus se-

quence comprises a null stimulus condition and a number of non-null stimulus conditions wherein said non-null stimulus conditions are presented at a lower frequency relative to said null stimulus condition.

[0015] In another preferred embodiment, the stimulus sequence is characterised by a sparse bipolar stimulus sequence, preferably a sparse bipolar visual stimulus sequence, containing three stimulus conditions or levels, the null condition, being represented by a baseline condition, and two relatively infrequently presented non-null stimulus conditions that are increments and decrements of a parameter about the vaseline condition. In this embodiment, the baseline condition suitably refers to a background stimulation level. For example, in the case of visual stimulation, the baseline condition may correspond to a background (or mean) luminance or brightness level.

[0016] In another preferred embodiment, the stimulus sequence is characterised by a sparse unipolar stimulus sequence containing a null stimulus condition and relatively infrequent occurrences of a non-null stimulus condition. For example, such a stimulus sequence may comprise a unipolar sparse visual stimulus sequence characterised by bright flashes only, which are presented relatively infrequently against a baseline brightness level.

[0017] Preferably, the step of presenting (step (a)) comprises: -dividing the visual field of view of each eye into a plurality of stimulus regions so as to roughly isolate confluent streams within the optic nerve, optic radiations and visual cortex due to their retinotopic arrangement and/or to stimulate different parts of areas of the brain concerned with vision; and -presenting to the two eyes stimuli having different temporal modulation of the appearance of each of the visual field of each eye, the stimuli being different for each of the corresponding regions within the visual field of view of each eye.

[0018] Preferably, the visual field is divided into quadrants partitioning the visual field along axes defining at least one member selected from the group consisting of the temporal, nasal, inferior and superior visual fields and concentrically organised partitions of these quadrants, which permits separate stimulation of central and peripheral parts of the visual field.

[0019] Preferably, in the above-preferred embodiment, the stimuli include modulation of the brightness or contrast of elements within each of the stimulus regions between two or three brightness levels or between two or three contrast levels.

[0020] Suitably, the temporally modulated stimuli are sufficiently complex so as to permit estimation of linear and non-linear weighting functions characterising the measured responses to each stimulus presented to each component part of the nervous system,

[0021] Preferably, the linear and non-linear weighting functions are Wiener or Volterra kernels.

[0022] Suitably, the latency to selected peaks within time course of linear kernels and/or the shape of the kernels or their amplitudes are used as measures of the functional status of component parts of the nervous system.

[0023] The non-null stimulus conditions within a stimulus sequence preferably occur with an average frequency of between about 1 and about 6 per second, more preferably between about 0.25 and about 6 per second. In an example of video stimulation at a frame rate of 50 Hertz this gives a probability of encountering the non-null stimulus of between about 1/2 and about 1/50.

[0024] In another aspect, there is an apparatus for assessing the functional status of component parts of the nervous system of a subject, comprising:

stimulation means for presenting to multiple component parts of the sensory nervous system of the subject stimulus sequences having different temporal modulation sequences of the appropriate stimulus modality for each stimulated part of the sensory nervous system, the stimuli having different sequences for each stimulated part, wherein the stimulation means comprises means-for fluctuating the temporally modulated stimuli between a null stimulus condition and at least one non-null stimulus condition selected from the group consisting of an increment stimulus condition and a decrement stimulus condition, relative to the null stimulus condition, wherein the probability of encountering the null stimulus condition in the stimulus sequences is higher compared to the probability of encountering the at least one non-null stimulus condition, and wherein the temporally modulated stimuli permit estimation of linear and non-linear weighting functions characterising measured responses to each stimulus presented to each component part of the nervous system;

means for estimating some or all of the coefficients of the linear and non-linear weighting functions for each stimulus sequence from the measured responses to the stimuli, to isolate separate responses from the separately and simultaneously stimulated component parts of the nervous system; and

means for estimating separate coefficients for responses to the other stimulus conditions to permit isolation of separate responses from component parts of the nervous system that respond to distinct members of the other stimulus conditions, characterised in that the at least one non-null condition occurs with an average frequency of between about 0.25 and about 25 per second and that the stimulus sequences comprise aperiodic or pseudorandom stimulus sequences.

[0025] The apparatus may further comprise monitoring means for monitoring responses to the stimulus sequences in the subject.

[0026] The coefficients of linear and non-linear weighting functions may be estimated for each stimulus sequence from the measured responses to the stimuli using a processing means.

[0027] The stimulation means suitably comprises

means for presenting a stream of separate, viewing images presented to each eye.

[0028] Suitably, the different viewing images comprise images of different contrast levels.

[0029] The monitoring means preferably comprises recordal means for recording responses to said stimulus sequences in said test subject.

[0030] Preferably, the recordal means records visual evoked potentials to provide an objective indication of the said responses.

[0031] The processing means suitably includes timing means and means for receiving signals from the recordal means indicative of said response.

BRIEF DESCRIPTION OF THE DRAWINGS

[0032]

Figure 1 is a functional block diagram of the basic system components forming a non-limiting embodiment of the apparatus of the invention for assessing the functional status of component parts of the nervous system.

Figure 2 illustrates four types of pseudorandom stimulus sequences. The upper panel illustrates a binary sequence where the stimulus varies between two levels. The central panel illustrates a ternary or bipolar version of a sparse pseudorandom stimulus sequence. In this instance, the stimulus has three levels including a more frequent null stimulus condition, at the middle stimulus level, and two less frequent stimulus conditions, at levels above and below the null stimulus condition. The third panel illustrates a more sparse ternary pseudorandom stimulus sequence. The fourth panel illustrates a unipolar very sparse pseudorandom stimulus sequence consisting of a unipolar non-null stimulus condition presented with randomly distributed interstimulus interval.

Figure 3 shows a schematic representation of the spatial layout of the visual stimulus used in a non-limiting embodiment of the apparatus of the invention.

Figure 4 shows Wiener kernel coefficients estimated for each of the eight regions of Figure 3. The left panel represents kernels from the 8 regions of Figure 3 when presented to the left eye. The right panel represents kernels obtained when the stimulus presentation was to the right eye.

Figure 5 is similar to Figure 4 except that the stimulus sequence was a sparse sequence of the type illustrated in the central panel of Figure 2 where the probability of generating the null stimulus condition was ½ and the probability of generating each of the other two conditions was ¼ each. The conventions are otherwise as in Figure 4.

Figure 6 is similar to Figures 3 and 4 except that the stimulus sequence is a sparse sequence of the type illustrated in the third panel of Figure 2 where the probability of generating the null stimulus condition was 14/16 and the probability of generating each of the other two conditions was 1/16 each. The conventions are otherwise as in Figure 4.

Figure 7 is similar to Figures 3, 4 and 5 except that the stimulus sequence is a unipolar very sparse sequence of the type illustrated in the lower panel of Figure 2 where the interstimulus interval was randomly distributed between 0.4 and 0.6 seconds. The conventions for left and right panels are otherwise as in Figure 4, that is, for presentation of the non-null stimulus to left and right eye respectively. The central panel illustrates Wiener kernels for presentation of the non-null stimulus condition to both eyes, that is, binocular presentation.

DETAILED DESCRIPTION

[0033] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which the invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, preferred methods and materials are described. For the purposes of the present invention, the following terms are defined below.

[0034] The articles *"a"* and *"an "* are used herein to refer to one or to more than one (i.e. to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

[0035] The term *"about "* is used herein to refer to frequencies or probabilities that vary by as much as 30%, preferably by as much as 20%, and more preferably by as much as 10% to a reference frequency or probability.

[0036] Throughout this specification, unless the context requires otherwise, the words *"comprise", "comprises"* and *"comprising"* will be understood to imply the inclusion of a stated step or element or group of steps or elements but not the exclusion of any other step or element or group of steps or elements.

[0037] The subject invention stems in part from the discovery that parts of the nervous system are controlled by mechanisms regulating their sensitivity and that some of these systems increase the response of the neurones they are regulating when stimuli appear infrequently compared to a baseline null stimulus condition. In this respect, the present inventors have found surprisingly that the low probability of encountering a stimulus differing from the baseline condition in sparse stimulus sequences insures that gain control mechanisms within the nervous system

will increase the neural response magnitude and also bias the measured responses to those neurone populations having such gain controls. They have also found that sparse aperiodic stimulus sequences can be used to characterise these increased responses by means of computing linear and non-linear temporal weighting functions such as Wiener or Volterra kernels. The consequently increased response amplitudes ensure more reliably recorded responses than are obtained with non-sparse stimuli. Biasing the response to those neural systems with gain controls biases neural assessment to dynamic neural systems that are likely to become defective in disease. In the case of stimulation of both eyes simultaneously, for example, the biasing of the response towards neural systems dominated by gain controls increases the symmetries of responses obtained from the left and right visual fields compared to responses observed for more conventional dense stimuli such as binary stimulus sequences. Accordingly, the use of sparse stimulus sequences provides more reliable assessment of neural systems that are subject to gain controls. In this connection, glaucoma is known to be a disease affecting retinal neurones embodying a strong, rapid, contrast gain control. More generally, assessment of neural function will be enhanced further by the accurate measurement of the time evolution of neural responses afforded by this invention.

[0038] The inventors have reduced their discoveries to practice in a method and apparatus for simultaneously assessing the functional status of component parts of the nervous system as described more fully hereinafter. Briefly, the method involves measuring linear and non-linear temporal weighting functions known as kernels that characterise the linear and non-linear stimulus evoked responses of component parts of the nervous system. The method employs particular stimulus sequences that not only have a temporal structure that is sufficiently complex to permit calculation of the requisite kernels, but that also have properties causing gain control mechanisms within the nervous system to generate larger and more reliable neural responses. These same stimuli should also permit separate measurement of responses generated within the nervous system to those parts of the stimulus sequences containing stimuli that are increments above and/or decrements below the average stimulus level or strength.

[0039] While the method can be applied to stimulation of any sensory modality, such as tactile or auditory stimuli to isolate responses from regions of the nervous system where these different sensory modalities are encoded, the visual stimulation is preferred. This is because of the large number of neurones in the visual pathway and the relative case with which these many neurones can be stimulated by the presentation of images to the eye. As well, the visual system produces observable stimulus evoked responses in the form of the pupil size and oculomotor activity.

[0040] Not wishing to be bound by any one particular theory, the reasoning that led to the development of the present invention is provided below.

[0041] As noted above Multi-stimulus Evoked Responses (MSERs) would likely be enhanced if the stimuli used would cause gain control mechanisms to enhance the reliability of the responses recorded. Also the clinical relevance of the recorded signals would be enhanced if recorded responses were biased towards those neural systems having such gain control mechanisms because neurological disease is likely to affect these gain control systems.

[0042] The visual nervous system is of particular interest because each optic nerve contains about one million nerve fibres and the majority of the brain is concerned with processing visual input. The visual inputs that carry information about luminance contrast in each part of the retinal image have a strong, rapidly acting gain control system as discussed in the paper by Benardete, E.A., et al., 1992, Vis Neurosci. 8(5): 483-486, entitled "Contrast gain control in the primate retina: P cells are not X-like, some M cells are". As discussed by those authors, this gain control system is manifested in retinal ganglion cells that project to the magnocellular layers of the dorsal lateral geniculate nucleus (dLGN), these retinal ganglion cells are thus referred to as M-cells. M-cells come in at least two varieties: the relatively more linearly responding MX-cells, and the more non-linearly responding MY-cells. The retinal gain control system acts so that responses to novel, visually large scale, stimuli are enhanced. Thus, in response to a step change in contrast over time, the neural response of the M-cells to the initial transient change is amplified and the response to the extended plateau part of the stop change in contrast diminishes rapidly in time as shown in the papers by J. D. Victor, entitled "The dynamics of the cat retinal Y cell subunit" (1988, J Physiol. (Lond). 405: 289-320), and "The dynamics of the cat retinal. X cell centre" (1987, J Physiol (Lond). 386: 219-246). The response to a single brief change in contrast is similarly enhanced. Such a single brief change in contrast which is too fast for a system to respond to anything more than the total time integrated energy of the stimulus is sometimes described as an impulsive stimulus. Such mechanisms may explain the enhancement of image contrast observed visually and in evoked potential, amplitudes in response to infrequently but periodically presented grating patterns as discussed by Kulikowski, J.J. ("Relation of psychophysics to, electrophysiology" Trace (Paris), 6: 64-69). Such periodic stimuli could not, however, be used to estimate Wiener or Volterra kernels.

[0043] Evidence has been presented for somewhat similar gain control mechanisms operating in other sensory modalities such as the somatosensory system by Brooke, J.D., et al. (1995, "Mechanisms within the human spinal cord suppress fast reflexes to control the movement of the legs", Brain Research 679: 255-260) and in the auditory nervous system by Boardman, I., et al. (1999, "Neural dynamics of perceptual order and context effects

for variable-rate speech syllables." Percept Psychophys. 61(8): 1477-1500).

[0044] In the visual system the M-type retinal ganglion cells can be placed into a relative high gain state by the frequency domain equivalent of a brief stimulus a continuous high frequency modulation of the contrast. One such example is that of the use of the spatial frequency doubling illusion for the diagnosis of glaucoma as discussed by James, A. C. and Maddess, T. in Australian Patent, No. 667,702 entitled "Glaucoma testing using non-linear systems identification techniques", by Maddess, T. in Australian Patent No. 611,585 entitled "Method and apparatus for use in diagnosis of glaucoma", and by Maddess, T. L. in Australian Patent No. 701,075 entitled "Early detection of glaucoma". The spatial frequency doubling illusion is an illusory visual percept that is seen when periodic grating patterns, having low spatial frequencies, have their contrast modulated, rapidly in time at a fixed high frequency, typically faster than 15 Hz. Under these conditions subjects report the periodic grating patterns as having twice as many stripes as are actually present, hence the name spatial frequency doubling (FD) illusion. The above patent documents hypothesise that the illusion is the product of a highly excited gain control mechanism expressed in the above mentioned non-linear MY retinal ganglion cells. A disadvantage of those methods is that such frequency domain methods provide information about the response of the nervous system to a single frequency. Also, visual mechanisms residing at the level of the visual cortex can interfere with persons ability to see the true FD effect produced by the retina (Maddess T. and Kulikowski, J. J., 1999, "Apparent fineness of stationary compound gratings" Vision Res. 39(20): 3404-16). Time domain tests would in principle provide a broader assessment of the nervous system since it will be understood by a person skilled in the art that such stimuli are effectively stimulating the nervous system with many frequencies at once and also permit estimation of the stimulus to response delay interval. The current method offers a way to measure MSERs with time, domain stimuli that, like the FD methods mentioned above, cause gain control mechanisms to provide enhanced neural responses. In addition the stimuli and method proposed provides other benefits in terms of reducing the variability of the evoked responses and enhancing their applicability for clinical assessment of the nervous system.

[0045] The convoluted surface of the cerebral cortex and other brain areas presents a problem when measuring SERs from the scalp in response to any type of sensory stimulus. The folding of these brain structures means that the electrical currents arising from brain activity sum together spatially so that signals available to be measured as surface potentials may be spatially distorted or uneven. In the visual system this translates into falsely distorted MSERs that do not accurately reflect the level of retinal responses in different parts of the retina as discussed in the paper by Klistorner, A., et al. (1988, "Multifocal topographic visual evoked potential: improving objective detection of local visual field defects" Invest Ophthalmol Vis Sci. 39(6): 937-950). Those authors attempted to ameliorate the problems caused by cortical folding by placing multiple electrodes on the scalp in a particular spatial configuration.

[0046] The left and right halves of the brain typically process sensory signals from their respective opposite sides of the body, although some overlap occurs, notably in the visual cortex, where neurones from the left and right eyes converge to produce binocular vision. It is worth noting that this convergence only serves to have binocular information about the right half of the visual field processed by the left visual cortex, and likewise, binocular information from the left half of the visual field processed by the right visual cortex. In a similar way maps of the somatosensory input from the body, and the auditory input from the world are present in different brain areas. Our ability to discern the details of the sensory input from surface recordings from these areas will be similarly affected by brain folding. The left and right halves of the brain are most often not folded in the same way and the naso-caudal mid-line of the brain may not always be precisely aligned with the mid-line of the head. Thus, brain folding and brain position within the head can potentially create left-right asymmetries in surface recordings from all sensory input to the two, halves of the visual field, ears or sides of the body. Obviously, all such distortions will limit the value of surface recordings, particularly MSERs, where one is attempting to distinguish responses from different component parts of the nervous system.

[0047] A possible method for partly resolving these asymmetries and distortions may arise from studying gain control mechanisms. In work leading up to the present invention, Maddess, T., et al. (1998, "Evidence for spatial aliasing effects in the Y-like cells of the magnocellular visual pathway" Vision Res. 38(12): 1843-1859) have shown that neurones relaying signals about retinal gain control mechanisms to the brain can be relatively sparse without compromising their function. In the case of MX and MY retinal ganglion cells a single gain control mechanism regulates the activity of both kinds of cells but only the less numerous MY-cells convey information about the gain control process to the brain. The more numerous MX-cells sample the retinal image densely, and the MY-cells sample the retinal image less densely. The authors showed that even though there are fewer MY-cells this might not compromise the brain's ability to understand what is happening to the gain of the more numerous MX cells. This economy of gain control encoding neurones is allowed if the gain control mechanism is based on measures of neural activity related to what engineers refer to as power. Each nerve fibre imposes a metabolic cost on the body so evolution will adopt mechanisms that insure tile minimum number of nerve fibres that permits the nervous system to operate accurately. Thus, it is likely that many sensory mechanisms

have similar economics in the number of neurones conveying information about gain control.

[0048] The relevance of this potential sparsity of nerve cells conveying gain control information around the nervous system is that, on the large brain areas were sensory information is represented as a largely contiguous map of the sensory input from the world, the gain control neurones will be sparsely spread across these maps. In this regard, Maddess, T., et al. (1998, Vision Res. 38(12): 1843-1859) have provided evidence that there are perhaps only 1 or 2 MY-cell inputs per cytochrome oxidase blob, a unit part of the visual cortex covering about a square millimetre of visual cortical surface in the human MX-cells may be of more direct interest in the present application but there are only about 5 to 10 times more of those neurones than MY-cells. Each MY-cell carries information about the gain of several MX-cells so cortical interpretation of gain changes to MX-cells may be organised with a sparseness comparable to MY-cell densities. These sparse arrays of neurones projected onto the cortex will, by definition, be unable to provide an accurate spatial representation of intricate brain foldings. As indicated by the above authors basic sampling theory tells us that providing the position of the gain control affected neurones is spatially random across the brain mapping the information arising from detailed brain foldings will be scattered into broad band noise, and thus have no average effect on the position of summed neural activity. This would lead to smaller effects of brain folding upon SERs measured from such cells. Similarly, left right asymmetries may also be reduced as the differential folding of the left and right halves of the brain may be of less impact.

[0049] Another way to enhance the applicability of stimuli for clinical assessment of the nervous system would be the ability to separately assess the response of the nervous system to stimuli that are either increments above or decrements below a continuous null stimulus. This is because separate classes of neurones within the nervous system are known to respond to either stimulus increments or decrements. In the visual nervous system groups of neurones responding separately to either increments or decrements of image brightness are well known as exemplified by Enroth-Cugell C., et al. (1980, "The contrast sensitivity of retinal ganglion cells of the cat" J Physiol (Lond). 304: 59-81). Cells responding to brightness increments are referred to as ON-units while those responding to brightness decrements are referred to as OFF-units. The previously mentioned MX and MY retinal ganglion cells come in ON and OFF classes.

[0050] The characteristic non-linear response component of MY-cells makes them respond in part to increments or decrements about equally, such a response quality being referred to as ON-OFF. This ON-OFF character is related to the gain control signal these neurones carry as discussed by Victor, J. D. (1988, *supra*) and so ON-OFF responses may in general reflect the presence of similar gain control mechanisms. This ON-OFF response quality is amenable to quantification by second order Wiener Volterra or similar kernels perhaps permitting more direct assessment of the operating condition of neural gain control systems. ON, OFF and ON-OFF responses to increments and decrements in stimulus strength are common features of the neurones of sensory nervous system for example being reported for neurones of the auditory nervous system by Cain, D. et al. (1999, "The effect of sound direction on frequency tuning in mouse inferior collicular neurones", Chin J Physiol. 42 (1): 1-8) and Bieser, A. et al. (1996, "Auditory responsive cortex in the squirrel monkey: neural responses to amplitude-modulated sounds" Exp Brain Res. 108(2): 273-84), and somatosensory brain by Leinonen, L. (1980, "Functional properties of neurones in the parietal retroinsular cortex in awake monkey", Acta Physiol Scand. 108(4): 381-4).

[0051] An efficient way to characterise the response of neurones is through the estimation of linear and non-linear weighting temporal functions known as kernels. These kernels can summarise linear response of the system under study and also non-linear interactions in the response. Multiple stimuli can be presented simultaneously and the responses to each characterised by separate kernels for each stimulus. For example, the present inventors in WO 99/49776 describe a method for estimating binocular interaction kernels and their potential use in diagnosing and monitoring diseases like multiple sclerosis.

[0052] From the foregoing, the present inventors considered that stimuli which could simultaneously be used to estimate kernels, and which caused neural gain control processes to enhance responses, and which permitted separate assessment of responses to stimuli containing increment and/or decrement stimuli from a prevailing baseline stimulus, and which might minimise the effects of brain folding, would provide efficient, non-invasive, assessment of broad sections of the nervous system.

[0053] Given the above the present inventors hypothesised that stimuli consisting of pseudorandom temporal, sequences consisting of a null stimulus condition, and other stimulus conditions representing increments or decrements from the null stimulus condition, and where the probability of encountering stimulus levels or qualities other than the baseline null stimulus condition was relatively low would provide the following:

(a) The temporally sparse nature of the increment and/or decrement stimuli would cause neural gain control mechanisms to enhance responses of those neural systems having such controls, much as single impulsive or step stimuli excite these mechanisms;

(b) The recorded responses arising from neural activity being biased towards such gain control mechanisms would thus bias the observed response towards mechanisms likely to be compromised by disease,

(c) The pseudorandom occurrence of the increments and decrements would make the stimuli sufficiently statistically rich as to permit the estimation of kernels in response to multiple stimuli thus making MSERs possible, even for quite short stimulus sequences;

(d) The presence of increments and decrements above and below the prevailing baseline stimulus condition would permit estimation of separate kernels for increment and decrement stimuli and to permit isolation of the separate responses of those neural mechanisms responding separately to increments and decrements.

[0054] In order that the invention may be readily understood and put into practical effect, particular preferred embodiments will now be described by way of the following non-limiting examples.

EXAMPLES

EXAMPLE 1

Apparatus

[0055] A schematic of the basic system components forming an embodiment of the apparatus of the present invention is shown in Figure 1. The major components are an apparatus for dichoptic stimulation of the two eyes, in the present non-limiting example by means (110) of a liquid crystal shutter, a means (102) for assessing cortical neural responses, in the present example electrodes, an amplifier (104) for recording a visual evoked electrical potential, and a means (106) for computing estimates of kernel coefficients. Thin arrows associate labels with objects while thick block arrows indicate the direction of information flow or control.

[0056] The test stimuli for each subject (100) were presented on a video monitor (108) at 101 pictures per second. Since the stimuli were presented on a video monitor (108) it is common to refer to the sequence of pictures presented-as a sequence of frames presented at a particular frame rate, in this case 101 frames per second. The stimulus sequence consisted of a stream of separate, but temporally interleaved, images presented alternately to each eye at 50:5 frames per second by use of a liquid crystal-shutter (110). Presentation of separate images to the two eyes is referred to as dichoptic presentation. To achieve dichoptic presentation of the stimuli to the two eyes the liquid crystal shutter (110) transmitted on alternate frames, light that is left or right circularly polarised, the changes in polarisation being synchronised to the picture presentation rate of 101 frames per second. Subjects (100) wore glasses where the element covering each eye transmitted only one of the two polarisations of the light transmitted through the shutter (110). In this way each eye saw only one of the two interleaved video sequences, each eye receiving pictures at 50.5 frames per second. Subjects (100) also wore normal corrective lenses as necessary. The total duration of the test sequences was 40 seconds and up to 8 sequences were presented to each subject.

[0057] Subjects (100) were asked to fixate a spot presented at the centre of the visual stimulus. Persons skilled in the art will recognise that other means of maintaining fixation, such as monitoring eye position could have been substituted without affecting the present demonstration. Evoked potentials were recorded with the samples being obtained synchronously with the rate of presentation of video stimuli. Faster sampling rates could have been used but for the present demonstration four sample per frame was used. Standard gold cup electrodes were placed on the scalp to record the evoked potentials. The dichoptic stimulus generation scheme and the VEP recording apparatus are illustrated in Figure 1. However, it should be noted that the present invention is not predicated on the use of any one particular means of recording evoked neuronal responses. In this regard, persons of skill in the art will recognise that evoked neuronal responses may be recorded by means other than be measuring electrical potentials such as by recording changes in magnetic, or electromagnetic radiation, or acoustic signals.

EXAMPLE 2

Pseudorandom stimulus sequences

[0058] The relevant feature of the sparse nature of the pseudorandom stimulus sequences will be better understood by inspection of Figure 2, which illustrates 4 types of pseudorandom stimulus sequences. The upper panel (A) illustrates a binary sequence where the stimulus varies between two levels. The stimulus was generated with a pseudorandom number generator with an even distribution and the probability of the stimulus being in either stimulus condition at a given time step was set to 1/2. The second panel (B) illustrates a ternary or bipolar version of a sparse pseudorandom stimulus sequence. Here the stimulus has three levels including a more frequent null stimulus condition, at the middle stimulus level, and two less frequent stimulus conditions, at levels above and below the null stimulus condition. In this case the probability of encountering the null condition was set to 1/2 and that of the other two states was set to 1/4. The third panel (C) illustrates a more sparse ternary pseudorandom stimulus sequence where the probability of the null state was set to 14/16 and of encountering the other two states was 1/16. It should be noted that the particular examples are eight-second sections of the actual 40-second stimulus and so the probabilities exhibited may not reflect those of the generating random process. The fourth panel (D) illustrates a unipolar very sparse stimulus sequence in which a single type of non-null stimulus condition is presented infrequently, with an interstimulus interval being always above a minimum value, chosen to

be above the duration of response to the stimulus condition. This lowest panel (D) represents a preferred but non-limiting embodiment of a sparse sequence. The stimulus sequences might just as well describe auditory stimuli where the stimulus conditions correspond to changes in sound pressure or frequency. Similarly the sequences might describe somatosensory stimuli such as changes in pressure level or frequency of a stimulus pressed against the skin or other tissue. The sparseness of the stimulus sequences would be appropriate to the modality stimulated. The stimulus sequences also do not have to have sharp rectangular transitions as shown in Figure 2 but may be smoothed in various ways and the temporal evolution of the departures from the null stimulus may be different for different non-null stimuli.

EXAMPLE 3

Visual stimulus

[0059] Figure 3 illustrates a visual stimulus for a particular non-limiting embodiment in which the face of a video monitor was divided into 8 parts demarked by the bold lines. In the tests described in the figures that follow subjects observed visual stimuli presented in each of the 8 regions and evoked potentials were recorded. The numbers in each of the eight regions shown will be used in the subsequent 3 figures to refer to these regions. Black and white checkerboard patterns were presented within each region, the boundaries of the checks being shown by the thin lines. Each region had its contrast modulated in time by different pseudorandom sequences each 40 s long. For the binary sequences of Figure 2 white checks are considered to have contrast 1 and black checks contrast -1. Thus the temporal modulation sequences caused the checks within each of the 8 regions to flip the sign of their contrast or remain the same contrast according to the state, 1 or -1, of the binary sequence at a given time step. For ternary stimuli the null stimulus condition for each of the regions was a uniform mid-level grey luminance, defined as having contrast zero; one of the non-null conditions had alternate black and white checks as in a checkerboard, defined as contrast 1; the other non-null condition reversed the contrast of the checks, white interchanging with black, and was defined as contrast level -1. The eight regions for each of the two eyes were modulated simultaneously in contrast according to independent stimulus sequences.. In separate recordings the three types of stimulus sequences illustrated in Figure 2 were used and in each case Wiener kernels were estimated from the evoked potentials.

EXAMPLE 4

Pseudorandom binary sequence A

[0060] With reference to Figure 4, the stimuli were pseudorandom binary sequences as shown in panel A of Figure 2. The left column represents kernels from the 8 regions of Figure 3 when presented to the left eye. The right column represents kernels obtained when the stimulus presentation was to the right eye. Each of the eight curves is the first off-diagonal of the second order self-quadratic Wiener kernel. The values of all points in all kernels are presented as voltage response, in units of microvolts as indicated by the scalebars. The pair of horizontal dotted lines for each kernel represents plus and minus 1.96 times the estimated standard error of the kernel, giving the critical region for a test of significance of the kernel values at the $\pm$95% confidence level. Thus, parts of the kernels that occur above or below these dotted lines are significant at the 95% level or better. The subject was a 20 year old female; kernels are calculated from eight repetitions of a 40 second stimulus. It should be noted that many of the quadratic kernels are not significant and that there is considerable difference in the kernels obtained for the left and right eyes.

EXAMPLE 5

Pseudorandom bipolar sequence B

[0061] Figure 5 shows similar information to Figure 4 but the stimulus sequence was a sparse sequence of the type illustrated in panel B of Figure 2 where the probability of generating the null stimulus condition was ½ and the probability of generating each of the other two conditions was ¼ each. The conventions are otherwise as in Figure 4. The data is from the same subject obtained in with the recordings interleaved between those that generated Figures 3 and 5. Notice that more of the kernels are significant than in Figure 4 and that the kernels from the two eyes are more similar than in Figures 3.

EXAMPLE 6

Pseudorandom bipolar sequence C

[0062] Figure 6 shows similar information to Figures 3 and 4 but the stimulus sequence is a sparse sequence of the type illustrated in panel C of Figure 2 where the probability of generating the null stimulus condition was 14/16 and the probability of generating each of the other two conditions was 1/16 each. The conventions are otherwise as in Figure 4. The data is from the same subject obtained in recordings interleaved between those that generated Figures 4 and 5. It should be noted that more of the quadratic kernels are significant than in either Figure 4 or 5 and that the kernels from the two eyes are more similar than in either Figure 4 or 5. Thus, as the stimulus sequences become steadily more sparse the reliability of the kernels increases.

EXAMPLE 7

Pseudorandom unipolar sequence D

[0063] Figure 7 shows similar information to Figures 4, 5 and 6 but the stimulus sequence is a unipolar very sparse sequence of the type illustrated in panel D of Figure 2 where one non-null stimulus condition is presented repeatedly with an interstimulus interval distributes between 0.4 and 0.6 seconds. The kernels plotted are the estimated first-order Wiener kernels, in units of microvolts as indicated by the scalebars. Dashed horizontal lines are drawn at plus and minus 1.96 times the estimated kernel standard errors, thus giving the critical region for a test of significance at the 95% confidence level. The data is from a 45-year-old female; kernels are calculated from 4 repeats of a 40-second stimulus sequence. In this figure left and right panels illustrate kernels pertaining to stimuli presented to left and right eyes respectively. The central panel illustrates kernels pertaining to presentation to both eyes, that is binocular presentation. Notice that large amplitude, highly significant kernels can be obtained from all regions, and from left eye, right eye and binocular presentation, all from a total of 4 times 40 seconds, that is 160 seconds of total recording time.

Claims

1. A method for simultaneously assessing the functional status of component parts of the nervous system of a subject, said method comprising:

   presenting simultaneously to multiple component parts of the sensory nervous system of the subject (100) stimulus sequences having different temporal modulation sequences of the appropriate stimulus modality for each stimulated part of the sensory nervous system, the stimuli having different sequences for each stimulated part;
   temporally modulating the stimuli between a null stimulus condition and at least one non-null stimulus condition selected from the group consisting of an increment stimulus condition and a decrement stimulus condition, relative to the nul stimulus condition, wherein the probability of encountering the null stimulus condition in the stimulus sequences is higher compared to the probability of encountering at least one non- null stimulus condition, and wherein the temporally modulated stimuli permit estimation of linear and non-linear weighting functions characterising measured responses to each stimulus presented to each component part of the nervous system;
   measuring responses to said stimulus sequences in said subject (100);
   estimating some or all of the coefficients of the linear and non-linear weighting functions for each stimulus sequence from the measured responses to said stimuli, to isolate separate responses from the separately and simultaneously stimulated component parts of the nervous system; and
   estimating separate coefficients for responses to said other stimulus conditions to permit isolation of separate responses from component parts of the nervous system that respond to distinct members of said other stimulus conditions;
   said method **characterised in that** said stimulus sequences are statistically independent pseudorandom stimulus sequences comprising an aperiodic null stimulus condition, the at least one sparse non-null stimulus condition occurs with average frequency of between about 0.25 and about 6 per second within a stimulus sequence.

2. The method of claim 1, **characterised in that** a stimulus sequence comprises a null stimulus condition and two non-null stimulus conditions comprising an increment stimulus condition **characterised by** an increment of a parameter relative to the null stimulus condition, and a decrement stimulus condition **characterised by** a decrement of a parameter relative to the null stimulus condition, wherein said non-null stimulus conditions are presented at a lower frequency relative to said null stimulus condition.

3. The method of claim 1, **characterised in that** a stimulus sequence comprises a null stimulus condition and a single non-null stimulus condition, wherein said non-null stimulus condition is presented at a lower frequency relative to said null stimulus condition.

4. The method of claim 1, **characterised in that** a stimulus sequence comprises a null stimulus condition and a number of non-null stimulus conditions wherein said non-null stimulus conditions are presented at a lower frequency relative to said null stimulus condition.

5. The method of claim 1, **characterised in that** the at least one non-null condition occurs with an average frequency of between about 1 and about 6 per second.

6. The method of claim 5, **characterised in that** the stimulation is selected from tactile stimuli, auditory stimuli, visual stimuli or a combination thereof.

7. The method of any of claims 1 to 6, **characterised in that** the at least one non-null condition comprises

stimulation by visual stimuli.

8. The method of any of claims 1 to 7, **characterised in that** the visual stimuli are selected from different luminance or contrast levels.

9. The method of claim 7, **characterised in that** a stimulus sequence comprises a null stimulus condition and two non-null stimulus conditions comprising an increment stimulus condition **characterised by** an increment of a parameter relative to the null stimulus condition, and a decrement stimulus condition **characterised by** a decrement of a parameter relative to the null stimulus condition, wherein said non-null stimulus conditions are presented at a lower frequency relative to said null stimulus condition.

10. The method of claim 9, **characterised in that** the parameter is relative stimulus contrast.

11. The method of claim 7, **characterised in that** a stimulus sequence comprises a null stimulus condition and a single non-null stimulus condition, wherein said non-null stimulus condition is presented at a lower frequency relative to said null stimulus condition.

12. The method of claim 11, **characterised in that** the parameter is luminance.

13. The method of claim 7, **characterised in that** the step of presenting comprises:

dividing the visual field of view of each eye of the subject into a plurality of stimulus regions so as to roughly isolate confluent streams within the optic nerve,
optic radiations and visual cortex due to their retinotopic arrangement and/or to stimulate different parts of areas of the brain concerned with vision; and
presenting to the two eyes stimuli having different temporal modulation of the appearance of each of the visual field of each eye, the stimuli being different for each of the corresponding regions within the visual field of view of each eye.

14. The method of claim 13, **characterised in that** the visual field is divided into quadrants partitioning the visual field along axes defining at least one member selected from the group consisting of the temporal, nasal, inferior and superior visual fields and concentrically organised partitions of these quadrants, which permits separate stimulation of central and peripheral parts of the visual field.

15. The method of claim 13 or claim 14, **characterised in that** the stimuli comprise modulation of the luminance or contrast of elements within each of the stimulus regions between two or three luminance levels or between two or three contrast levels.

16. The method of claim 15, **characterised in that** the function governing alternation between the levels is approximately uniformly distributed noise.

17. The method of claim 15, **characterised in that** the stimuli comprise modulation of an additional parameter selected from the group or position, or apparent depth of colour of elements of the stimulus zones between two or three levels and the function governing alternation between the levels is approximately uniformly distributed noise.

18. The method of any of claims 1-17, **characterised in that** the temporally modulated stimuli are sufficiently complex so as to permit estimation of linear and non-linear weighting functions characterising the measured responses to each stimulus presented to each component part of the nervous system.

19. The method of any of claims 1-18, **characterised in that** the linear and non-linear weighting functions are Wiener or Volterra kernels.

20. The method of claim 19, **characterised in that** the latency to selected peaks within time course of linear kernels and/or the shape of the kernels or their amplitudes are used as measures of the functional status of component parts of the nervous system.

21. An apparatus for assessing the functional status of component parts of the nervous system of a subject (100), comprising:

stimulation means (108, 110) for presenting simultaneously to multiple component parts of the sensory nervous system of the subject (100) stimulus sequences having different temporal modulation sequences of the appropriate stimulus modality for each stimulated part of the sensory nervous system, the stimuli having different sequences for each stimulated part, wherein the stimulation means comprises means (110) for temporally modulating stimuli between a null stimulus condition and at least one non-null stimulus condition selected from the group consisting of an increment stimulus condition and a decrement stimulus condition, relative to the null stimulus condition, wherein the probability of encountering the null stimulus condition in the stimulus sequences is higher compared to the probability of encountering the at least one non-null stimulus condition, and wherein the temporally modulated stimuli permit estimation of linear and non-linear weighting functions characterising

measured responses to each stimulus presented to each component part of the nervous system;

monitoring means (102, 104) for measuring responses to said stimulus sequences in said subject (100);

means for estimating some or all of the coefficients of the linear and non-linear weighting functions for each stimulus sequence from the measured responses to said stimuli, to isolate separate responses from the separately and simultaneously stimulated component parts of the nervous system; and

means for estimating separate coefficients for responses to said other stimulus conditions to permit isolation of separate responses from component parts of the nervous system that respond to distinct members of said other stimulus conditions; said apparatus **characterised in that** said stimulus sequences are statistically independent pseudorandom stimulus sequences comprising an aperiodic null stimulus condition, and said stimulation means (108, 110) comprises means for presenting the at least one sparse non-null condition at an average frequency of between about 0.25 and about 6 per second within a stimulus sequence.

22. The apparatus of claim 21, wherein said coefficients of linear and non-linear weighting functions are estimated for each stimulus sequence from the measured responses to said stimuli using a processing means.

23. The apparatus of claim 21, **characterised in that** the stimulation means (108, 110) comprises means for presenting a stimulus sequence comprising a null stimulus condition and two non-null stimulus conditions comprising an increment stimulus condition **characterised by** an increment of a parameter relative to the baseline stimulus condition, and a decrement stimulus condition **characterised by** a decrement of a parameter relative to the null stimulus condition, wherein said non-null stimulus conditions are presented at a lower frequency relative to said null stimulus condition.

24. The apparatus of claim 21, **characterised in that** the stimulation means (108, 110) comprises means for presenting a stimulus sequence comprises a null stimulus condition and a single non-null stimulus condition, wherein said non-null stimulus condition is presented at a lower frequency relative to said null stimulus condition.

25. The apparatus of claim 21, **characterised in that** the stimulation means (108, 110) comprises means for presenting the at least one non-null condition at an average frequency of between about 1 and about 6 per second.

26. The apparatus of any of claim 21 to 25, **characterised in that** the stimulation means (108, 110) comprises means for stimulating a sensory modality.

27. The apparatus of claim 21 to 26, **characterised in that** the stimulation means (108, 110) comprises means for stimulating the visual senses.

28. The apparatus of claim 21 to 27, **characterised in that** the stimulation means (108, 110) comprises means for presenting different luminance levels.

29. The apparatus of claim 21 to 28, **characterised in that** the stimulation means (108,110) comprises means for presenting different contrast levels.

30. The apparatus of claim 21 to 29, **characterised in that** the stimulation means (108, 110) comprises means for presenting a stream of separate, viewing images presented to each eye.

31. The apparatus of claim 3 0, **characterised in that** the separate viewing images comprise images of different contrast levels.

32. The apparatus of claim 30, **characterised in that** the separate viewing images comprise images of different luminance levels.

33. The apparatus of any of claims 30 to 32, **characterised in that** the stimulation means (108, 110) comprises means for presenting to each eye a plurality of stimulus regions so as to roughly isolate confluent streams within the optic nerve, optic radiations and visual cortex due to their retinotopic arrangement and/or to stimulate different parts of areas of the brain concerned with vision.

34. The apparatus of any of claims 30 to 33, **characterised in that** the stimulation means (108, 110) further comprises means for presenting to the two eyes stimuli having different temporal modulation of the appearance of each of the visual field of each eye, the stimuli being different for each of the corresponding regions within the visual field of view of each eye.

35. The apparatus of claim 34, **characterised in that** the visual field is divided into quadrants partitioning the visual field along axes defining at least one member selected from the group consisting of the temporal, nasal, inferior and superior visual fields and concentrically organised partitions of these quadrants, which permits separate stimulation of central and peripheral parts of the visual field.

36. The apparatus of any of claims 21 to 35, **characterised in that** the monitoring means comprises recordal means for recording responses to said stimulus sequences in said test subject.

37. The apparatus of claim 36, **characterised in that** the recordal means records visual evoked potentials to provide an objective indication of said responses.

38. The apparatus of any of claims 21 to 37, **characterised in that** the processing means comprises timing means and means for receiving signals from the recordal means indicative of said response.

Patentansprüche

1. Verfahren zum gleichzeitigen Beurteilen des funktionellen Zustands von Komponententeilen des Nervensystems eines Subjekt, wobei das Verfahren aufweist:

gleichzeitiges Darbieten von Stimulus-Sequenzen an eine Mehrzahl von Komponententeilen des sensorischen Nervensystems des Subjekts (100) mit verschiedenen zeitlichen Modulationssequenzen der passenden Stimulus-Modalität für jeden stimulierten Teil des sensorischen Nervensystems, wobei die Stimuli verschiedene Sequenzen für jeden stimulierten Teil aufweisen,

zeitliches Modulieren der Stimuli zwischen einem Nullstimuluszustand und mindestens einem von null verschiedenen Stimuluszustand, der ausgewählt ist aus der Gruppe, die gebildet wird von einem zunehmenden Stimuluszustand und einem abnehmenden Stimuluszustand relativ zu dem Nullstimuluszustand, wobei die Wahrscheinlichkeit, dass der Nullstimuluszustand in den Stimulus-Sequenzen auftritt, höher ist verglichen mit der Wahrscheinlichkeit, dass mindestens ein von Null verschiedener Stimuluszustand auftritt, und wobei die zeitlich modulierten Stimuli eine Abschätzung von linearen und nicht-linearen Wichtungsfunktionen erlauben, die gemessene Reaktionen auf jeden Stimulus, der jedem Komponententeil des Nervensystems dargeboten wird, charakterisieren,

Messen von Reaktionen auf die Stimulus-Sequenzen in dem Subjekt (100) Abschätzen einiger oder aller der Koeffizienten der linearen und nicht-linearen Wichtungsfunktionen für jede Stimulus-Sequenz aus den gemessenen Reaktionen auf die Stimuli, um getrennte Reaktionen von den getrennt und gleichzeitig stimulierten Komponententeilen des Nervensystems zu isolieren, und

Abschätzen von getrennten Koeffizienten für Reaktionen auf die anderen Stimuluszustände, um eine Isolation von getrennten Reaktionen von Komponententeilen des Nervensystems zu ermöglichen, die auf verschiedene Elemente der anderen Stimuluszustände reagieren,

wobei das Verfahren **dadurch gekennzeichnet ist, dass** die Stimulus-Sequenzen statistisch unabhängige pseudo-zufällige Stimulus-Sequenzen sind mit einem aperiodischen Nullstimuluszusfiand, wobei der mindestens eine seltene von null verschiedene Stimuluszustand mit einer mittleren Frequenz zwischen 0,25 und ungefähr 6 mal pro Sekunde in einer Stimulus-Sequenz auftritt.

2. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, dass** eine Stimulus-Sequenz einen Nullstimuluszustand und zwei von null verschiedene Stimuluszustände mit einem zunehmenden Stimuluszustand, der durch ein Zunehmen eines Parameters relativ zu dem Nullstimuluszustand **gekennzeichnet** ist, und einem abnehmenden 5fiimuluszusiand, der durch ein Abnehmen eines Parameters relativ zu dem Nullstimuluszustand **gekennzeichnet** ist, aufweist, wobei die von null verschiedenen Stimuluszustände bei einer geringeren Frequenz relativ zu dem Nullstimuluszustand angelegt werden.

3. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, dass** eine Stimulus-Sequenz einen Nullstimuluszustand und einen einzigen von null verschiedenen Stimuluszustand aufweist, wobei der von null verschiedene Stimuluszustand mit einer geringeren Frequenz relativ zu dem Nullstimuluszustand dargeboten wird.

4. Verfahren nach Anspruch 9, **dadurch gekennzeichnet, dass** eine Stimulus-Sequenz einen Nullstimuluszustand und eine Anzahl von von null verschiedenen Stimuluszuständen aufweist, wobei die von null verschiedenen Stimuluszustände mit einer geringeren Frequenz relativ zu dem Nullstimuluszustand dargeboten werden.

5. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, dass** der mindestens eine von null verschiedene Zustand mit einer mittleren Frequenz zwischen ungefähr 1 und ungefähr 6 pro Sekunde auftritt.

6. Verfahren nach Anspruch 5, **dadurch gekennzeichnet, dass** die Stimulation ausgewählt ist aus taktiler Stimulation, auditiver Stimulation, visueller Stimulation oder einer Kombination davon.

7. Verfahren nach einem der Ansprüche 1 bis 6, **dadurch gekennzeichnet, dass** mindestens ein von null verschiedener Zustand eine Stimulation durch

visuelle Stimuli aufweist.

8. Verfahren nach einem der Ansprüche 1 bis 7, **dadurch gekennzeichnet, dass** die visuellen Stimuli ausgewählt sind aus verschiedenen Leuchtkraft- oder Kontrastniveaus.

9. Verfahren nach Anspruch 7, **dadurch gekennzeichnet, dass** eine Stimulus-Sequenz einen Nullstimuluszustand und zwei von null verschiedene Stimuluszustände mit einem zunehmenden Stimuluszustand, der durch ein Zunehmen eines Parameters relativ zu dem Nullstimuluszustand **gekennzeichnet** ist, und einem abnehmenden Stimuluszustand, der **gekennzeichnet ist durch** ein Abnehmen eines Parameters relativ zu dem Nullstimuluszustand, aufweist, wobei die von null verschiedenen Stimuluszustände mit einer geringeren Frequenz relativ zu dem Nullstimuluszustand dargeboten werden.

10. Verfahren nach Anspruch 9, **dadurch gekennzeichnet, dass** der Parameter ein relativer Stimuluskontrast ist.

11. Verfahren nach Anspruch 7, **dadurch gekennzeichnet, dass** eine Stimulus-Sequenz einen Nullstimuluszustand und einen einzigen von null verschiedenen Stimuluszustand aufweist, wobei der von null verschiedene Stimuluszustand mit einer geringeren Frequenz relativ zu dem Nullstimuluszustand dargeboten wird.

12. Verfahren nach Anspruch 11, **dadurch gekennzeichnet, dass** der Parameter die Beleuchtungsstärke ist.

13. Verfahren nach Anspruch 7, **dadurch gekennzeichnet, dass** der Schritt des Darbietens aufweist:

    Teilen des visuellen Sichtfeldes jedes Auges des Subjekts in eine Mehrzahl von Stimulusbereiche, so dass konfluente Ströme innerhalb des optischen Nervs, der optischen Strahlungen und der visuellen Kortex aufgrund ihrer retinotopischen Anordnung isoliert werden und/oder so dass verschiedene Teile von Bereichen des Gehirns die mit dem Sehen beschäftigt sind, stimuliert werden.

14. Verfahren nach Anspruch 13, **dadurch gekennzeichnet, dass** das Sichtfeld in Quadranten geteilt wird, die das Sichtfeld entlang von Achsen einteilen, die mindestens ein Element bilden, das ausgewählt ist aus der Gruppe, die besteht aus den Schläfen-, den Nasen-, den inferioren und den superioren visuellen Felder und durch konzentrisch organisierte Teilungen dieser Quadranten, die eine getrennte Stimulation von zentralen und peripheren Teilen des Sichtfelds ermöglichen.

15. Verfahren nach Anspruch 13 oder 14, **dadurch gekennzeichnet, dass** die Stimuli eine Modulation der Beleuchtungsstärke oder des Kontrasts von Elementen innerhalb der Sfiimulatiansbereiche zwischen zwei oder drei Beleuchtungsstärkeniveaus oder zwischen zwei oder drei Kontrastniveaus aufweisen.

16. Verfahren nach Anspruch 15, **dadurch gekennzeichnet, dass** die Funktion, welche einen Wechsel zwischen den Niveaus regelt, ungefähr gleichmäßig verteiltes Rauschen ist.

17. Verfahren nach Anspruch 15, **dadurch gekennzeichnet, dass** die Stimuli eine Modulation eines zusätzlichen Parameters aufweisen, der ausgewählt ist aus der Gruppe oder der Position oder einer offensichtlichen Farbtiefe von Elementen der Stimuluszonen zwischen zwei oder drei Niveaus und die Funktion, welche einen Wechsel zwischen den Niveaus regelt, ungefähr gleichförmig verteiltes Rauschen ist.

18. Verfahren nach einem der Ansprüche 1 bis 17, **dadurch gekennzeichnet, dass** die zeitlich modulierten Stimuli ausreichend komplex sind, so dass sie eine Abschätzung von linearen und nicht-linearen Wichtungsfunktionen, welche die gemessenen Reaktionen auf jeden Stimulus, der jedem Komponententeil des Nervensystems dargeboten wird, charakterisieren.

19. Verfahren nach einem der Ansprüche 1 bis 18, **dadurch gekennzeichnet, dass** die linearen und nicht-linearen Wichungsfunktionen Wiener- oder Volterra-Kerne sind.

20. Verfahren nach Anspruch 19, **dadurch gekennzeichnet, dass** die Latenz für ausgewählte Spitzen innerhalb des Zeitverlaufs von linearen Kernen und/oder die Form der Kerne oder ihrer Amplituden als Maß des funktionellen Zustands der Komponententeile des Nervensystems verwendet werden.

21. Vorrichtung zum Bewerten des funktionellen Zustands von Komponententeilen des Nervensystems eines Subjekts (10) mit
einem Stimulationsmittel (108, 110) zum gleichzeitigen Darbieten an eine Mehrzahl von Komponententeilen des sensorischen Nervensystems des Subjekts (100) von Stimulus-Sequenzen mit verschiedenen zeitlichen Modulationssequenzen der passenden Stimulusmodalität für jeden stimulierten Teil des sensorischen Nervensystems, wobei die Stimuli verschiedene Sequenzen für jeden stimulierten Teil aufweisen, wobei das Stimufationsmittel ein

Mittel (110) aufweist zum zeitlichen Modulieren von Stimuli zwischen einem Nullstimuluszustand und mindestens einem von null verschiedenen Stimuluszustand, der ausgewählt ist aus der Gruppe, die aus einem zunehmenden Stimuluszustand und einem relativ zu dem Nullstimuluszustand abnehmenden Stimuluszustand besteht, wobei die Wahrscheinlichkeit des Auftretens des Nullstimuluszustandes in den Stimulus-Sequenzen höher ist verglichen mit der Wahrscheinlichkeit des Auftretens des mindestens einen von null verschiedenen Stimuluszustands, und wobei die zeitlich modulierten Stimuli eine Abschätzung von linearen und nicht-linearen Wichtungsfunktionen erlauben, die gemessene Reaktionen auf jeden Stimulus charakterisieren, der jedem Komponententeil des Nervensystems dargeboten wird,
einem Überwachungsmittel (102, 104) zum Messen von Reaktionen auf die Stimulussequenzen in dem Subjekt (100),
einem Mittel zum Abschätzen einiger oder aller der Koeffizienten der linearen und nicht-linearen Wichtungsfunktionen für jede Stimulussequenz aus den gemessenen Reaktionen auf die Stimuli, um getrennte Reaktionen von getrennten und gleichzeitig stimulierten Komponententeilen des Nervensystems zu isolieren, und
einem Mittel zum Abschätzen von getrennten Koeffizienten für Reaktionen auf die anderen Stimuluszustände, um ein Isolieren von getrennten Reaktionen von Komponententeilen des Nervensystems, die auf verschiedene Elemente der anderen Stimuluszustände reagieren, zu ermöglichen,
wobei die Vorrichtung **dadurch gekennzeichnet ist, dass** die Stimulussequenzen statistisch unabhängige, pseudo-zufällige Stimulussequenzen mit einem aperiodischen Nullstimuluszustand sind, und das Stimulationsmittel (108, 110) ein Mittel zum Darbieten des mindestens einen seltenen von null verschiedenen Zustands mit einer mittleren Frequenz zwischen ungefähr 0,25 und ungefähr 6 pro Sekunde innerhalb einer Stimulussequenz aufweist.

22. Vorrichtung nach Anspruch 21, wobei die Koeffizienten von linearen und nicht-linearen Wichungsfunktionen für jede Stimulussequenz aus den gemessenen Reaktionen auf die Stimuli abgeschätzt wird, wobei ein Verarbeitungsmittel verwendet wird.

23. Vorrichtung nach Anspruch 21, **dadurch gekennzeichnet, dass** das Stimulationsmittel (108, 110) ein Mittel aufweist zum Darbieten einer Stimulussequenz mit einem Nullstimuluszustand und zwei von null verschiedenen Stimutuszuständen mit einem zunehmenden Stimuluszustand, der durch eine Zunahme eines Parameters relativ zu der Basislinie Stimuluszustand **gekennzeichnet** ist, und einem abnehmenden Stimuluszustand, der durch eine Abnahme eines Parameters relativ zu dem Nullstimuluszustand **gekennzeichnet** ist, wobei die von null verschiedenen Stimuluszustände mit einer geringeren Frequenz relativ zu dem Nullstimuluszustand dargeboten werden.

24. Vorrichtung nach Anspruch 21, **dadurch gekennzeichnet, dass** das Stimulationsmittel (108, 110) ein Mittel zum Darbieten einer Stimulussequenz mit einem Nullstimuluszustand und einem einzigen von null verschiedenen Stimuluszustand aufweist, wobei der von null verschiedene Stimuluszustand mit einer geringeren Frequenz relativ zu dem Nullstimuluszustand dargeboten wird.

25. Vorrichtung nach Anspruch 21, **dadurch gekennzeichnet, dass** das Stimulationsmittel (108, 110) ein Mittel zum Darbieten des mindestens einen von null verschiedenen Zustands mit einer mittleren Frequenz zwischen ungefähr 1 und ungefähr 6 pro Sekunde aufweist.

26. Vorrichtung nach einem der Ansprüche 21 bis 25, **dadurch gekennzeichnet, dass** das Stimulationsmittel (108, 110) ein Mittel zum Stimulieren einer sensorischen Modalität aufweist.

27. Vorrichtung nach einem der Ansprüche 21 bis 26, **dadurch gekennzeichnet, dass** das Stimulationsmittel (108, 110) ein Mittel zum Stimulieren der visuellen Sinne aufweist.

28. Vorrichtung nach einem der Ansprüche 21 bis 27, **dadurch gekennzeichnet, dass** das Stimulationsmittel (108, 110) ein Mittel zum Darbieten verschiedener Beleuchtungsstärkeniveaus aufweist.

29. Vorrichtung nach einem der Ansprüche 21 bis 28, **dadurch gekennzeichnet, dass** das Stimulationsmittel (108, 110) ein Mittel zum Darbieten verschiedener Kontrastniveaus aufweist.

30. Vorrichtung nach einem der Ansprüche 21 bis 29, **dadurch gekennzeichnet, dass** das Stimulationsmittel (108, 110) ein Mittel zum Darbieten eines Stroms von getrennten Betrachtungsbilder, die jedem Auge dargeboten werden, aufweist.

31. Vorrichtung nach Anspruch 30, **dadurch gekennzeichnet, dass** die getrennten Betrachtungsbilder verschiedene Kontrastniveaus aufweisen.

32. Vorrichtung nach Anspruch 30, **dadurch gekennzeichnet, dass** die getrennten Betrachtungsbilder verschiedene Beleuchtungsstärkeniveaus aufweist.

33. Vorrichtung nach einem der Ansprüche 30 bis 32, **dadurch gekennzeichnet, dass** das Stimulations-

mittel (108, 110) ein Mittel zum Darbieten einer Mehrzahl von Stimulusbereichen an jedes Auge aufweist, so dass in etwa isolierte konfluente Ströme innerhalb des optischen Nerven, der optischen Strahlungen und der visuellen Kortex aufgrund ihrer retinotopischen Anordnung isoliert werden und/oder verschiedene Teile von Bereichen des Gehirns, die mit dem Sehen beschäftigt sind, stimuliert werden.

34. Vorrichtung nach einem der Ansprüche 30 bis 33, **dadurch gekennzeichnet, dass** das Stimulationsmittel (188, 110) darüber hinaus ein Mittel zum Darbieten von Stimuli an die beiden Augen aufweist, die eine verschiedene zeitliche Modulation des Aussehens jedes
der visuellen Felder des Auges aufweisen, wobei die Stimuli für jeden aus den entsprechenden Bereichen innerhalb des visuellen Sichtfeldes jedes Auges verschieden sind.

35. Vorrichtung nach Anspruch 34, **dadurch gekennzeichnet, dass** das visuelle Feld in Quadranten geteilt ist, die das visuelle Feld entlang von Achsen, welche mindestens ein Element bilden, das aus der Gruppe ausgewählt ist, die besteht aus den Schläfen-, den Nasal-, den inferioren und den superioren visuellen Feldern, und konzentrisch isolierten Teilungen dieser Quadranten, die eine getrennte Stimulation von zentralen und peripheren Teilen des visuellen Feldes ermöglichen.

36. Vorrichtung nach einem der Ansprüche 21 bis 35, **dadurch gekennzeichnet, dass** das Überwachungsmittel ein Aufzeichnungsmittel zum Aufzeichnen von Reaktionen auf die Stimulussequenzen in dem Testsubjekt aufweist

37. Vorrichtung nach Anspruch 36, **dadurch gekennzeichnet, dass** das Aufzeichnungsmittel visuell hervorgerufene Potentiale aufzeichnet, um eine objektive Darstellung der Reaktionen bereitzustellen.

38. Vorrichtung nach einem der Ansprüche 21 bis 37, **dadurch gekennzeichnet, dass** das Verarbeitungsmittel ein Mittel zur Zeithaltung und ein Mittel zum Empfangen von Signalen, welche die Reaktion bezeichnen, von dem Aufzeichnungsmittel aufweist.

Revendications

1. Procédé visant à évaluer simultanément l'état fonctionnel de parties composant le système nerveux d'un sujet, ledit procédé comprenant :

la présentation simultanée à de multiples composants du système nerveux sensoriel du sujet (100) de séquences de stimuli, ayant des séquences de modulation temporelle différentes, selon le mode de stimulus approprié pour chaque partie stimulée du système nerveux sensoriel, les stimuli ayant des séquences différentes pour chaque partie stimulée ;
la modulation dans le temps des stimuli entre une condition de stimulus nulle et au moins une condition de stimulus non-nulle choisie dans le groupe constitué d'une condition de stimulus incrémentée et d'une condition de stimulus diminuée,
relativement à la condition de stimulus nulle, dans lequel la probabilité de rencontrer la condition de stimulus nulle dans les séquences de stimulation est supérieure à la probabilité de rencontrer au moins une condition de stimulus non-nulle, et dans lequel les stimuli modulés dans le temps permettent d'estimer les fonctions de pondération linéaire et non-linéaire caractérisant les réponses mesurées à chaque stimulus présenté à chaque composant du système nerveux :

la mesure des réponses auxdites séquences de stimulus chez ledit sujet (100) ;
l'estimation de certains ou de tous les coefficients des fonctions de pondération linéaires et non-linéaires pour chaque séquence de stimulus à partir des réponses mesurées auxdits stimuli, afin d'isoler des réponses séparées des parties de composants du système nerveux stimulées séparément et simultanément ; et
l'estimation de coefficients séparés pour des réponses auxdites autres conditions de stimulus, afin de permettre l'isolation de réponses séparées des parties de composants du système nerveux qui répondent à des éléments distincts desdites autres conditions de stimulus ; ledit procédé étant **caractérisé en ce que** lesdites séquences de stimulus sont statistiquement des séquences de stimulus pseudo-aléatoires indépendantes, comprenant une condition de stimulus nulle apériodique,
ladite au moins une condition de stimulus non-nulle éparse survenant avec une fréquence moyenne comprise entre environ 0,25 et environ 6 par seconde dans une séquence de stimulus.

2. Procédé selon la revendication 1, **caractérisé en ce qu'**une séquence de stimulus comprend une condition de stimulus nulle et deux conditions de stimulus non-nulles comprenant une condition de stimulus incrémentée, **caractérisée par** une augmentation d'un paramètre relatif à la condition de stimulus nulle, et une condition de stimulus diminuée, **caractérisée**

par une diminution d'un paramètre relatif à la condition de stimulus nulle, dans lequel lesdites conditions de stimulus non-nulles sont présentées à une fréquence inférieure relativement à ladite condition de stimulus nulle.

3. Procédé selon la revendication 1, **caractérisé en ce qu'**une séquence de stimulus comprend une condition de stimulus nulle et une seule condition de stimulus non-nulle, dans lequel ladite condition de stimulus non-nulle est présentée à une fréquence inférieure relativement à ladite condition de stimulus nulle.

4. Procédé selon la revendication 1, **caractérisé en ce qu'**une séquence de stimulus comprend une condition de stimulus nulle et un certain nombre de conditions de stimulus non-nulles dans lequel lesdites conditions de stimulus non-nulles sont présentées à une fréquence inférieure relativement à ladite condition de stimulus nulle.

5. Procédé selon la revendication 1, **caractérisé en ce que** ladite au moins une condition non-nulle survient avec une fréquence moyenne comprise entre environ 1 et environ 6 par seconde.

6. Procédé selon la revendication 5, **caractérisé en ce que** la stimulation est choisie parmi des stimuli tactiles, des stimuli auditifs, des stimuli visuels ou une combinaison de ceux-ci.

7. Procédé selon l'une quelconque des revendications 1 à 6, **caractérisé en ce que** ladite au moins une condition non-nulle comprend une stimulation par stimuli visuels.

8. Procédé selon l'une quelconque des revendications 1 à 7, **caractérisé en ce que** les stimuli visuels sont choisis parmi différents niveaux de luminance ou de contraste.

9. Procédé selon la revendication 7, **caractérisé en ce qu'**une séquence de stimulus comprend une condition de stimulus nul et deux conditions de stimulus non-nulles comprenant une condition de stimulus incrémentée, **caractérisée par** une augmentation d'un paramètre relativement à la condition de stimulus nulle, et une condition de stimulus décrémentée, **caractérisée par** une diminution d'un paramètre relativement à la condition de stimulus nulle, dans lequel lesdites conditions de stimulus non-nulles sont présentées à une fréquence inférieure relativement à ladite condition de stimulus nulle.

10. Procédé selon la revendication 9, **caractérisé en ce que** le paramètre est un contraste de stimulus relatif.

11. Procédé selon la revendication 7, **caractérisé en ce qu'**une séquence de stimulus comprend une condition de stimulus nulle et une seule condition de stimulus non-nulle, dans lequel ladite condition de stimulus non-nulle est présentée à une fréquence inférieure relativement à ladite condition de stimulus nulle.

12. Procédé selon la revendication 11, **caractérisé en ce que** le paramètre est la luminance.

13. Procédé selon la revendication 7, **caractérisé en ce que** l'étape de présentation comprend :

la division du champ de vision visuel de chaque oeil du sujet en une pluralité de régions de stimulus, de façon à isoler grossièrement les courants confluents dans le nerf optique, les radiations optiques et le cortex visuel du fait de leur disposition rétinotopique et/ou à stimuler différentes parties ou zones du cerveau concernées par la vision ; et
la présentation aux deux yeux de stimuli ayant une modulation différente dans le temps de l'aspect de chacun des champs visuels de chaque oeil, les stimuli étant différents pour chacune des zones correspondantes dans le champ de vision visuel de chaque oeil.

14. Procédé selon la revendication 13, **caractérisé en ce que** le champ visuel est divisé en cadrans séparant le champ visuel le long d'axes définissant au moins un élément choisi dans le groupe constitué des champs temporel, nasal, visuel supérieur et inférieur et des séparations organisées concentriquement de ces cadrans, ce qui permet une stimulation séparée des parties centrale et périphériques du champ visuel.

15. Procédé selon la revendication 13 ou la revendication 14, **caractérisé en ce que** les stimuli comprennent la modulation de la luminance ou du contraste des éléments dans chacune des zones de stimulus entre deux ou trois niveaux de luminance ou entre deux ou trois niveaux de contraste.

16. Procédé selon la revendication 15, **caractérisé en ce que** la fonction régissant l'alternance entre les niveaux est un bruit réparti de manière approximativement uniforme.

17. Procédé selon la revendication 15, **caractérisé en ce que** les stimuli comprennent la modulation d'un paramètre supplémentaire choisi dans le groupe ou la position, ou la profondeur apparente de couleur des éléments des zones de stimulus entre deux ou trois niveaux et la fonction régissant l'alternance entre les niveaux est un bruit réparti de manière ap-

proximativement uniforme.

18. Procédé selon l'une quelconque des revendications 1-17, **caractérisé en ce que** les stimuli modulés dans le temps sont suffisamment complexes pour permettre l'estimation de fonctions de pondération linéaires et non-linéaires caractérisant les réponses mesurées à chaque stimulus présenté à chaque partie de composant du système nerveux.

19. Procédé selon l'une quelconque des revendications 1-18, **caractérisé en ce que** les fonctions de pondération linéaire et non-linéaire sont des noyaux de Wiener ou Volterra.

20. Procédé selon la revendication 19, **caractérisé en ce que** la latence aux pics choisis pendant le laps de temps des noyaux linéaires et/ou la forme des noyaux ou leur amplitude sont utilisés comme des mesures de l'état fonctionnel des composants du système nerveux.

21. Appareil visant à évaluer l'état fonctionnel de composants du système nerveux d'un sujet (100) comprenant :

des moyens de stimulation (108, 110) pour présenter simultanément à de multiples composants du système nerveux sensoriel du sujet (100), des séquences de stimuli ayant des séquences de modulation temporelle différentes, selon le mode de stimulus appropriée pour chaque partie stimulée du système nerveux sensoriel, les stimuli ayant des séquences différentes pour chaque partie stimulée, dans lequel les moyens de stimulation comprennent des moyens (110) pour moduler dans le temps les stimuli entre une condition de stimulus nulle et au moins une condition de stimulus non-nulle, choisie dans le groupe constitué d'une condition de stimulus incrémentée et d'une condition de stimulus diminuée, relativement à la condition de stimulus nulle, dans lequel la probabilité de rencontrer la condition de stimulus nulle dans les séquences de stimulus est supérieure à la probabilité de rencontrer ladite au moins une condition de stimulus non-nulle, et dans lequel les stimuli modulés dans le temps permettent l'estimation de fonctions de pondération linéaires et non-linéaires caractérisant des réponses mesurées à chaque stimulus présenté à chaque composant du système nerveux ;
des moyens de contrôle (102, 104) pour mesurer les réponses auxdites séquences de stimulus dans ledit sujet (100) ;
des moyens pour estimer certains ou tous les coefficients des fonctions de pondération linéaires et non-linéaires pour chaque séquence de stimulus, à partir des réponses mesurées auxdits stimuli, afin d'isoler des réponses séparées des composants stimulés séparément et simultanément du système nerveux ; et
des moyens pour estimer des coefficients séparés pour des réponses auxdites autres conditions de stimulus, afin de permettre l'isolation de réponses séparées provenant des composants du système nerveux qui répondent à des éléments distincts desdites autres conditions de stimulus ; ledit appareil étant **caractérisé en ce que** lesdites séquences de stimulus sont des séquences de stimulus pseudo-aléatoires statistiquement indépendantes comprenant une condition de stimulus nulle apériodique, et lesdits moyens de stimulation (108, 110) comprennent des moyens pour présenter ladite au moins une condition non-nulle éparse à une fréquence moyenne comprise entre environ 0,25 et environ 6 par seconde dans une séquence de stimulus.

22. Appareil selon la revendication 21, dans lequel lesdits coefficients de fonctions de pondération linéaire et non-linéaires sont estimés pour chaque séquence de stimulus à partir des réponses mesurées auxdits stimuli en utilisant un moyen de traitement.

23. Appareil selon la revendication 21, **caractérisé en ce que** les moyens de stimulation (108, 110) comprennent des moyens pour présenter une séquence de stimulus comprenant une condition de stimulus nulle et deux conditions de stimulus non-nulles, comprenant une condition de stimulus incrémentée, **caractérisée par** une augmentation d'un paramètre relativement à la condition de stimulus de base, et une condition de stimulus diminuée, **caractérisée par** une diminution d'un paramètre relativement à la condition de stimulus nulle, dans lequel lesdites conditions de stimulus non-nulles sont présentées à une fréquence inférieure à ladite condition de stimulus nulle.

24. Appareil selon la revendication 21, **caractérisé en ce que** les moyens de stimulation (108, 110) comprennent des moyens pour présenter une séquence de stimulus comprenant une condition de stimulus nulle et une seule condition de stimulus non-nulle, dans lequel ladite condition de stimulus non-nulle est présentée à une fréquence inférieure à ladite condition de stimulus nulle.

25. Appareil selon la revendication 21, **caractérisé en ce que** les moyens de stimulation (108, 110) comprennent des moyens pour présenter ladite au moins une condition non-nulle à une fréquence moyenne entre environ 1 et environ 6 par seconde.

26. Appareil selon l'une quelconque des revendications

21 à 25, **caractérisé en ce que** les moyens de stimulation (108, 110) comprennent des moyens pour stimuler une modalité sensorielle.

27. Appareil selon la revendication 21 à 26, **caractérisé en ce que** les moyens de stimulation (108, 110) comprennent des moyens pour stimuler les sensations visuelles.

28. Appareil selon la revendication 21 à 27, **caractérisé en ce que** les moyens de stimulation (108, 110) comprennent des moyens pour présenter différents niveaux de luminance.

29. Appareil selon la revendication 21 à 28, **caractérisé en ce que** les moyens de stimulation (108, 110) comprennent des moyens pour présenter différents niveaux de contraste.

30. Appareil selon la revendication 21 à 29, **caractérisé en ce que** les moyens de stimulation (108, 110) comprennent des moyens pour présenter un courant d'images de visualisation séparées, présentées à chaque oeil.

31. Appareil selon la revendication 30, **caractérisé en ce que** les images de visualisation séparées comprennent des images de niveaux de contraste différents.

32. Appareil selon la revendication 30, **caractérisé en ce que** les images de visualisation séparées comprennent des images de niveaux de luminance différents.

33. Appareil selon l'une quelconque des revendications 30 à 32, **caractérisé en ce que** les moyens de stimulation (108, 110) comprennent des moyens pour présenter à chaque oeil une pluralité de zones de stimulus, de façon à isoler grossièrement les courants confluents dans le nerf optique, les radiations optiques et le cortex visuel du fait de leur disposition rétinotopique et/ou à stimuler différentes parties des zones du cerveau concernées par la vision.

34. Appareil selon l'une quelconque des revendications 30 à 33, **caractérisé en ce que** les moyens de stimulation (108, 110) comprennent en outre des moyens pour présenter aux deux yeux, des stimuli ayant une modulation différente dans le temps de l'aspect de chacun des champs visuels de chaque oeil, les stimuli étant différent pour chacune des zones correspondantes dans le champ de vision visuel de chaque oeil.

35. Appareil selon la revendication 34, **caractérisé en ce que** le champ visuel est divisé en cadrans séparant le champ visuel, le long d'axes définissant au moins un élément choisi dans le groupe constitué des champs visuels temporel, nasal et visuel inférieur et supérieur et des séparations organisées de manière concentrique de ces cadrans, qui permet une stimulation séparée des parties centrale et périphérique du champ visuel.

36. Appareil selon l'une quelconque des revendications 21 à 35, **caractérisé en ce que** les moyens de contrôle comprennent des moyens d'enregistrement pour enregistrer les réponses auxdites séquences de stimulus dans ledit sujet test.

37. Appareil selon la revendication 36, **caractérisé en ce que** les moyens d'enregistrement enregistrent les potentiels évoqués visuels pour donner une indication objective desdites réponses.

38. Appareil selon l'une quelconque des revendications 21 à 37, **caractérisé en ce que** les moyens de traitement comprennent des moyens de temporisation et des moyens pour recevoir des signaux des moyens d'enregistrement indicatifs de ladite réponse.

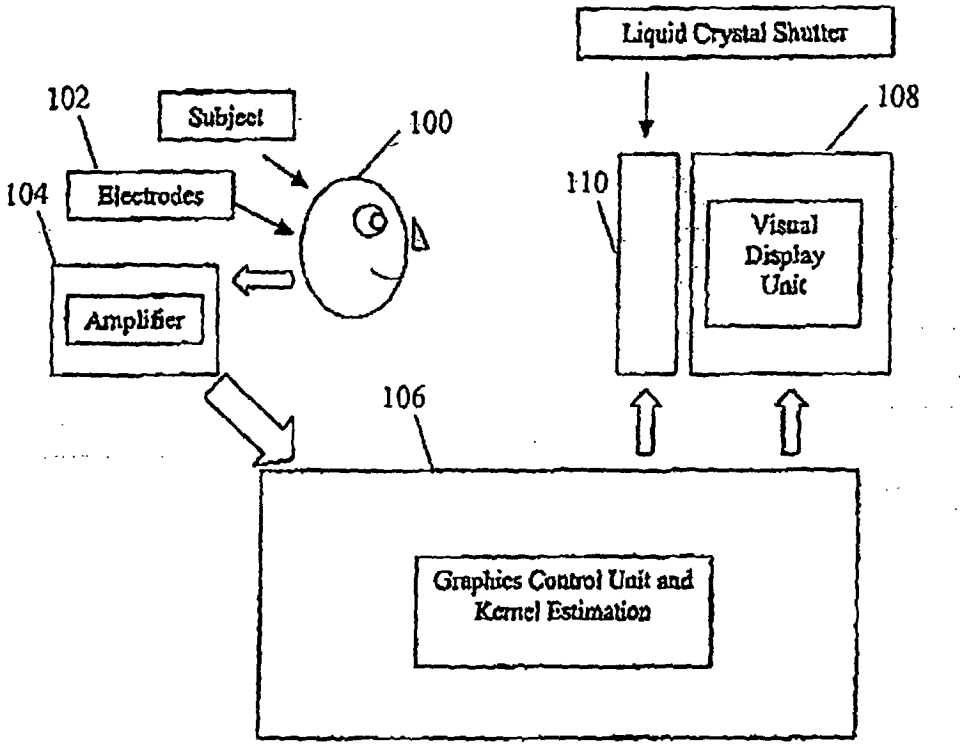
Liquid Crystal Shutter
102
Subject
100
108
104
Electrodes
110
Visual
Display
Unit
Amplifier
106
Graphics Control Unit and
Kernel Estimation

FIGURE 1

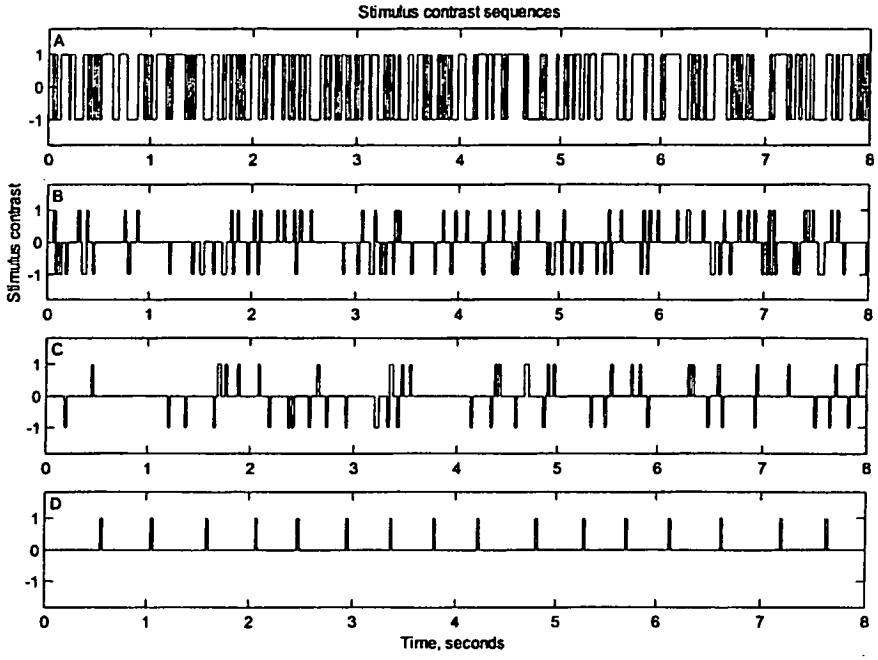
Stimulus contrast sequences
A
B
C
D
Stimulus contrast
1
0
-1
0
1
2
3
4
5
6
7
8
Time, seconds

FIGURE 2

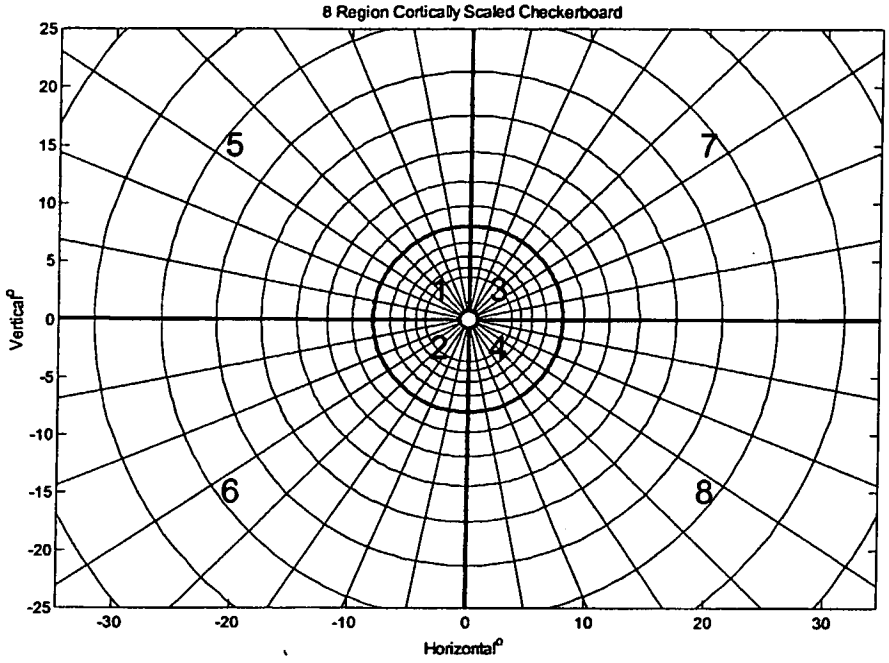
8 Region Cortically Scaled Checkerboard
Vertical°
Horizontal°
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
-20
-10
0
10
20
30
1
2
3
4
5
6
7
8

FIGURE 3

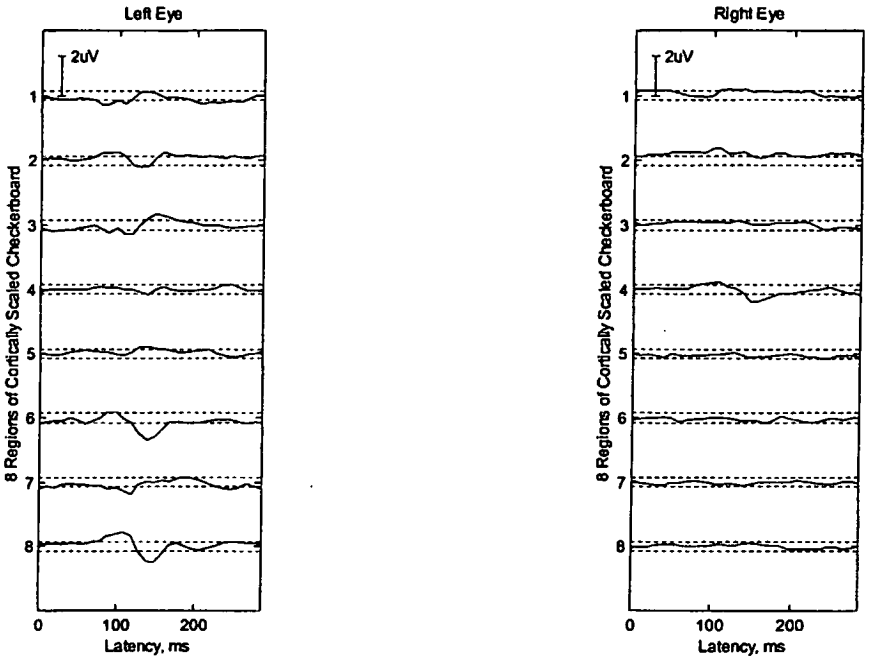
Left Eye
2uV
1
2
3
4
5
6
7
8
8 Regions of Cortically Scaled Checkerboard
0
100
200
Latency, ms
Right Eye
2uV
1
2
3
4
5
6
7
8
8 Regions of Cortically Scaled Checkerboard
0
100
200
Latency, ms

FIGURE 4

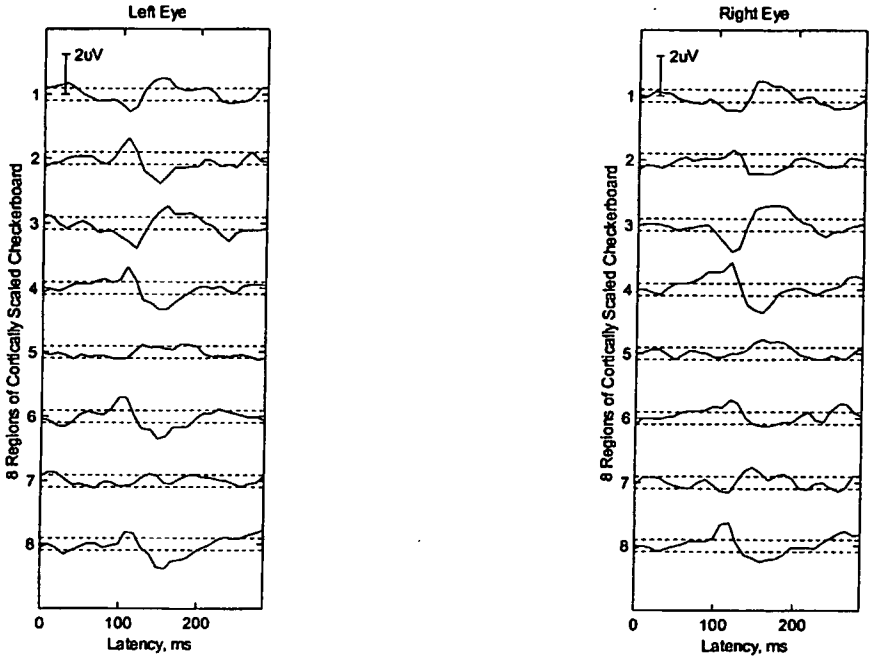
Left Eye
2uV
1
2
3
4
5
6
7
8
8 Regions of Cortically Scaled Checkerboard
0
100
200
Latency, ms
Right Eye
2uV
1
2
3
4
5
6
7
8
8 Regions of Cortically Scaled Checkerboard
0
100
200
Latency, ms

FIGURE 5

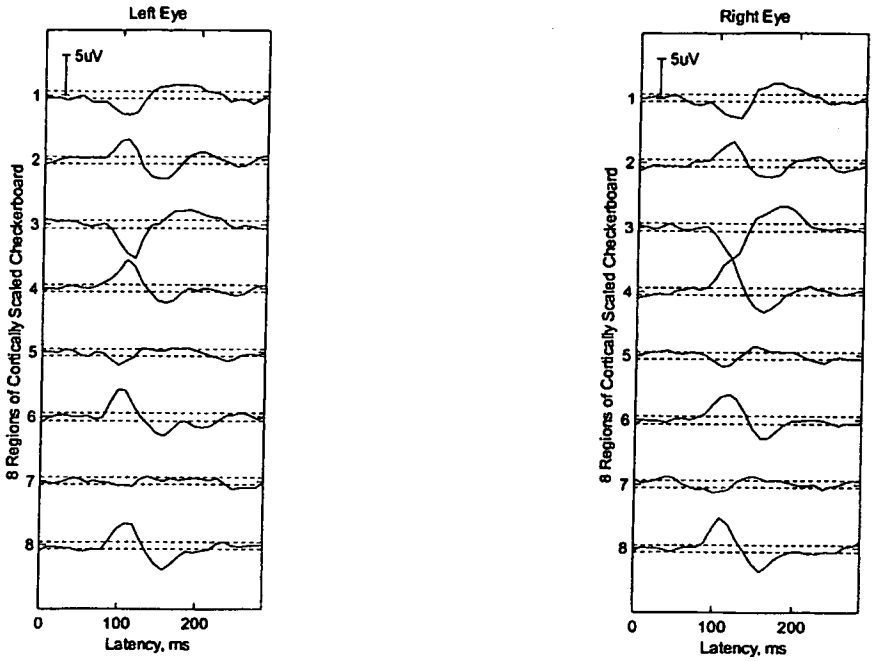
Left Eye
5uV
1
2
3
4
5
6
7
8
8 Regions of Cortically Scaled Checkerboard
0
100
200
Latency, ms
Right Eye
5uV
1
2
3
4
5
6
7
8
8 Regions of Cortically Scaled Checkerboard
0
100
200
Latency, ms

FIGURE 6

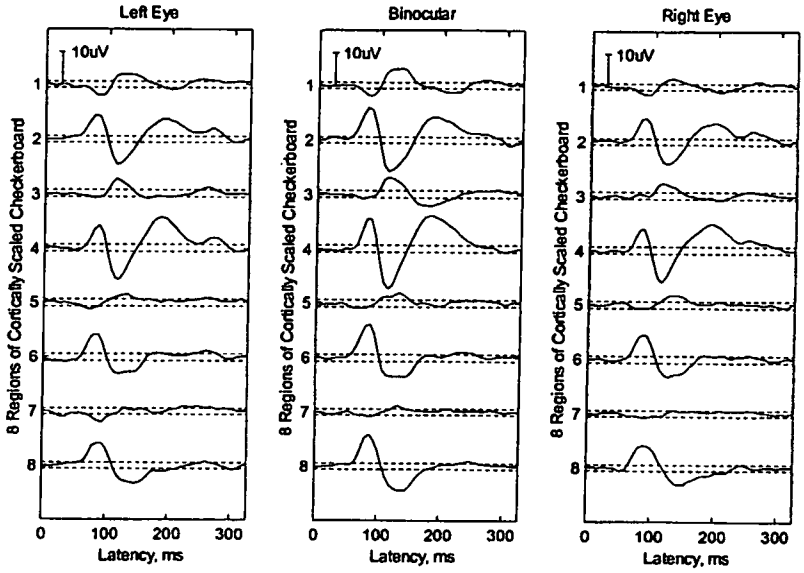
Left Eye
Binocular
Right Eye
10uV
8 Regions of Cortically Scaled Checkerboard
1
2
3
4
5
6
7
8
0
100
200
300
Latency, ms

FIGURE 7

REFERENCES CITED IN THE DESCRIPTION

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专利名称(译)	用于通过稀疏刺激评估神经功能的方法和设备		
公开(公告)号	EP1267703B1	公开(公告)日	2010-11-17
申请号	EP2001916739	申请日	2001-03-27
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IPC分类号	A61B3/00 A61B5/00 A61B5/0484 A61B3/10 A61B5/04		
CPC分类号	A61B5/04842 A61B5/4064		
代理机构(译)	HARDING，CHARLES THOMAS		
优先权	2000PQ6465 2000-03-27 AU		
其他公开文献	EP1267703A4 EP1267703A1		
外部链接	Espacenet		

摘要(译)

本发明涉及一种通过向感觉神经系统的一个或多个部分提供稀疏刺激来同时评估神经系统组成部分的功能状态的方法和设备。 稀疏刺激由相对于基准零刺激条件呈现的刺激条件的时间序列组成，其中非零刺激条件或条件相对不频繁地呈现。 在稀疏刺激序列中遇到与基线或无效刺激条件不同的刺激的可能性很小，从而确保了神经系统内的增益控制机制将增加神经反应的幅度，并对具有这种增益控制的那些神经元群体偏向于所测得的反应。 因此，与非稀疏刺激相比，增加的响应幅度可确保更可靠地记录响应。

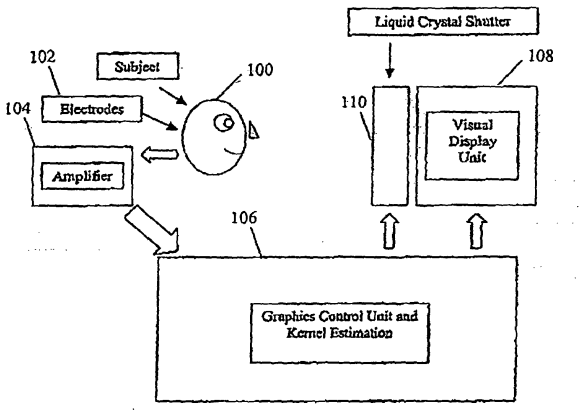

FIGURE 1