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(54) **TRANSLATIONAL SENSORY STIMULATION
PROCEDURE FOR THE STIMULATION OF
AMYGDALA-HIPPOCAMPAL COMPLEX**

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(57) **ABSTRACT**

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The present invention relates to a methods and systems for the stimulation of the amygdala-hippocampal complex of a subject by a translational sensory stimulation procedure based on one or more time-series of random sensory pulses. Furthermore, it relates to methods for the representation of the neural activity of the amygdala-hippocampal complex of a subject.

Figure 1

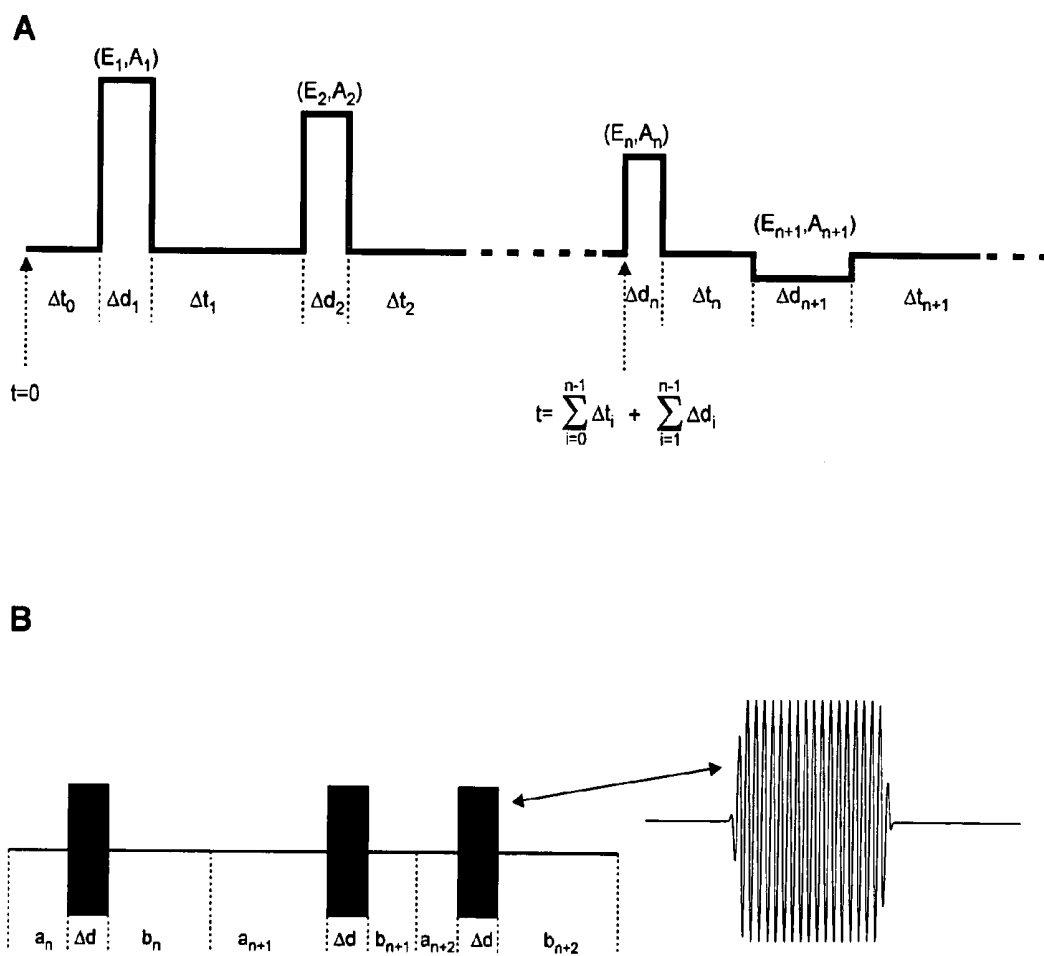


Figure 2

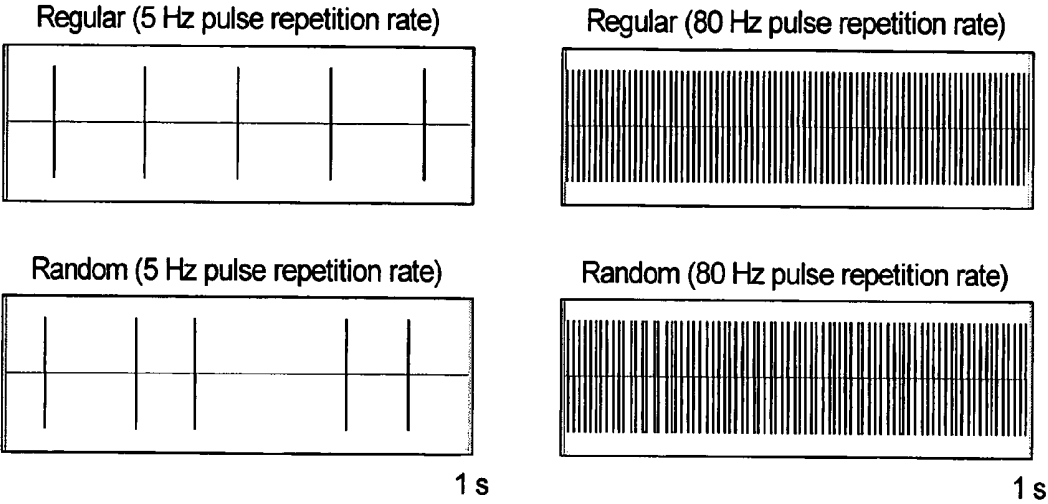
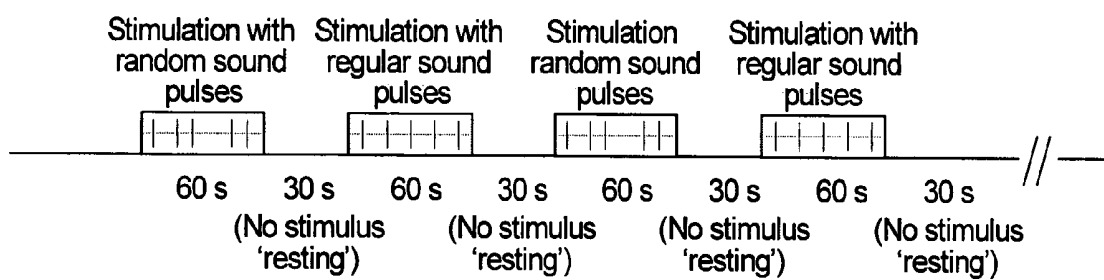


Figure 3



Time line of block-design stimulation paradigm (e.g. 20 min) during fMRI data acquisition

Figure 4

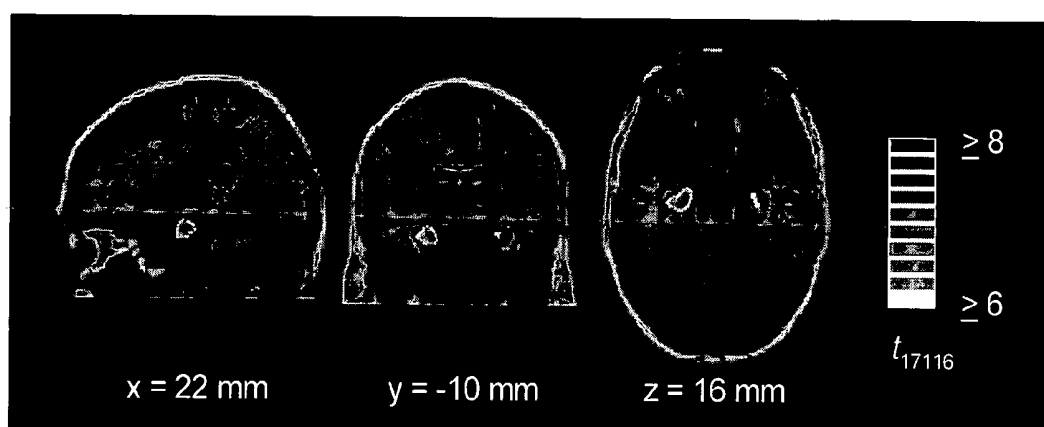


Figure 5

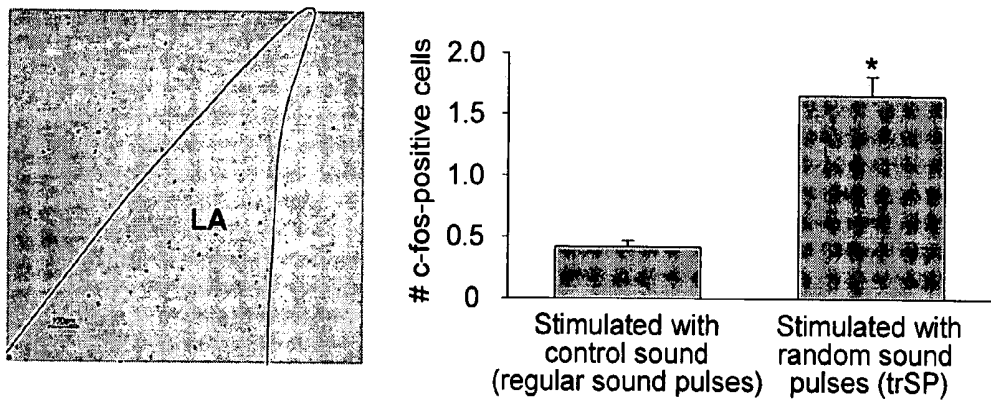


Figure 6

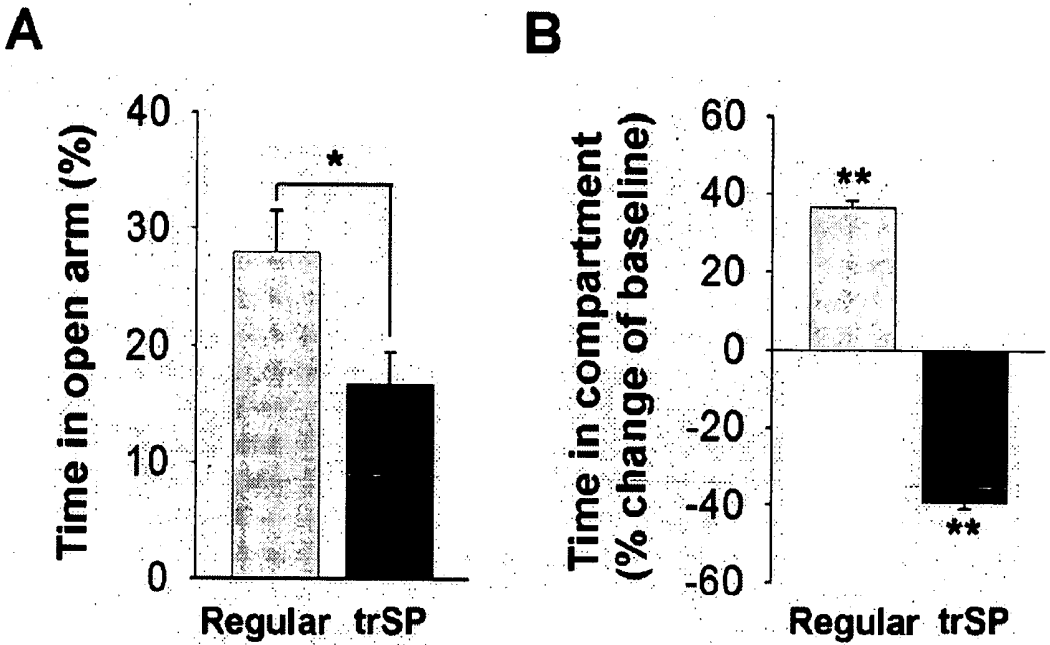
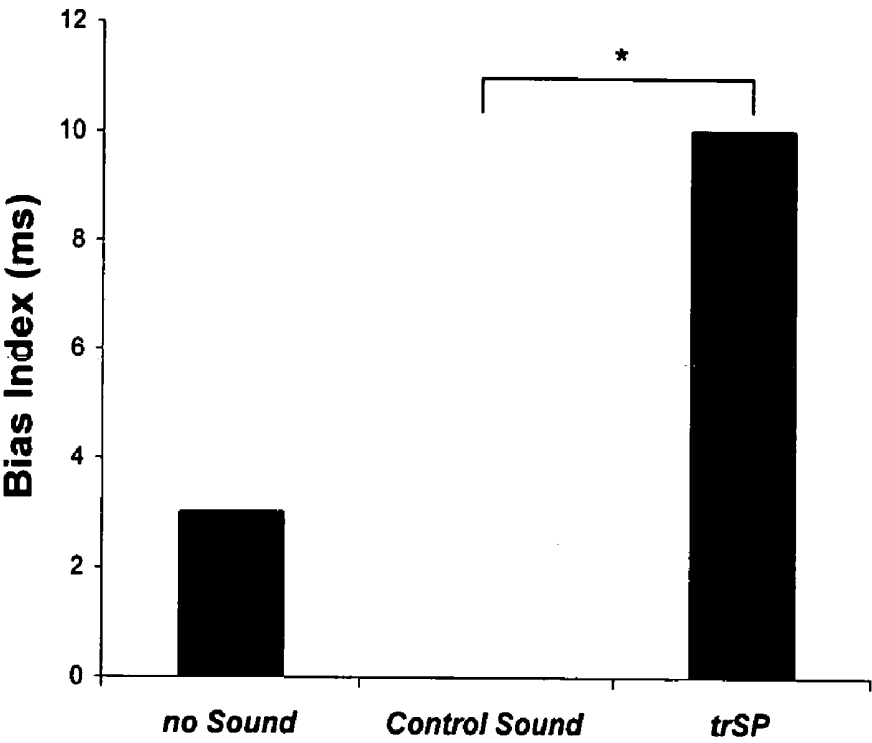


Figure 7



TRANSLATIONAL SENSORY STIMULATION PROCEDURE FOR THE STIMULATION OF AMYGDALA-HIPPOCAMPAL COMPLEX

[0001] This application claims the benefit of European Application No. EP 04 003 858, filed Feb. 22, 2004, the content of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to a novel method and to a novel system for the stimulation of the amygdala-hippocampal complex of a subject by a translational sensory stimulation procedure based on one or more time-series of random sensory pulses. Furthermore, it relates to a novel method for the representation of the neural activity of the amygdala-hippocampal complex of a subject.

BACKGROUND

[0003] The amygdala-hippocampal complex is a key structure in the mammalian brain that mediates emotional and related processes. The amygdala-hippocampal complex is increasingly considered as a brain structure whose physiological functions are disturbed in affective (depression) and anxiety disorders as well as related disorders such as schizophrenia, personality disorder, addiction and other mental health conditions. It plays a central role in emotional memory formation, fear processing, emotional recognition, social functions and associative learning mechanisms. Understanding the function of the amygdala-hippocampal complex is one of the major targets in cognitive neuroscience in humans and animals, and represents an important target of functional genomics as well as drug development for psychiatric conditions.

[0004] The publications and other materials used herein to illustrate the invention and, in particular, to provide additional details respecting the practice are incorporated by reference.

[0005] While current studies concentrate either on mechanisms in the human or in the animal brain, true translational approaches, which are approaches that relate mechanisms in humans to mechanisms in animals and vice versa, remain scarce. However, it is considered that translational research or translational neuroscience is an important route to understanding and treating human disease conditions (Society for Neuroscience: Translational Neuroscience Accomplishments. Society for Neuroscience (<http://web.sfn.org/content/Publications/TranslationalNeuroscience/-translational.pdf>), 2003)). In fact, translational research represents probably one of the most promising approaches to a better understanding of mental health conditions. While in humans, brain functions and dysfunctions can be studied in the target species, the possibilities to challenge and study such processes are limited. Translational studies using animal models allow going a step ahead, including electrophysiological, pharmacological and molecular approaches. A major problem in translational studies, however, is that functional probes usually vary significantly between human and animal experiments, which reduces the translational comparability and limits the inferences that can be carried from humans to animals and from animals to humans. For example, neural mechanisms in the amygdala of animals are classically studied using fear-conditioning experiments, in which a

fear-inducing stimulus (e.g. an electrical foot shock), the unconditioned stimulus, is combined with a neutral stimulus (e.g. a soft tone), the conditioned stimulus. Such and other stimulation paradigms are reviewed by LeDoux (Annu Rev Neurosci 2000; 23:155-84). Obviously, this approach is quite limited in human research, especially in humans with affective or anxiety problems. On the other hand, amygdala and amygdala-hippocampal complex activation studies in humans are typically based on stimuli accessing higher cognitive or social functions including emotionally valenced pictures (e.g. angry faces) and other suitable stimulation paradigms as described by Zald (Brain Res Rev 2003; 41:88-123).

[0006] Although the common denominator of classical probes used in animals and humans is neural activity within the amygdala-hippocampal complex, the mechanisms that lead to this effect may be quite different and thus are comparable in a translational view only with significant limitations.

[0007] In addition, previously used stimulation approaches to activate the amygdala-hippocampal complex are based on stimuli that have an intrinsic emotional value to the subject exposed to the stimulus like e.g. emotionally valenced pictures, aversive sounds, pain, infant cries or laughs and the like. Furthermore, typical current approaches for stimulating the amygdala-hippocampal complex in humans and animals have the disadvantage that the subject gets habituated to the stimulus after a short period of time like approximately 2-10 seconds as described by Breiter et al. (Neuron 1996; 17:875-87) and Bordi and LeDoux (J Neurosci 1992; 12:2493-503). Thus, known stimuli are losing their amygdala-hippocampal complex-stimulating properties across repetitive applications over time leading to transient but not persistent neural activity alteration. A specific disadvantage of this transient neural response of the amygdala-hippocampal complex is that experimental studies during altered neural activity state of the amygdala-hippocampal complex are limited.

[0008] Thus there is a need for an approach for the stimulation of the amygdala-hippocampal complex, which does not have an intrinsic emotional value. There is also a need for an approach for the stimulation of the amygdala-hippocampal complex that is not habituating and thus consistent. There is also a need for stimulating the amygdala-hippocampal complex in a human or non-human animal in a consistent fashion to influence behavioral patterns.

SUMMARY OF THE INVENTION

[0009] According to the invention the amygdala-hippocampal complex of a subject is stimulated by a method comprising generating and transmitting a translational sensory stimulation procedure based on one or more time-series of random sensory pulses to said subject, which alters the neural activity of said amygdala-hippocampal complex of said subject.

[0010] The invention is also directed to a method for stimulating an amygdala-hippocampal complex of a subject. The method comprises the generation and transmission of a translational sensory stimulation procedure (trSP) based on one or more time-series of random sensory pulses to the subject, wherein the trSP alters the neural activity of said amygdala-hippocampal complex of the subject so that an

amygdala-hippocampal complex-dependent physiological function is created. The amygdala-hippocampal complex-dependent physiological function may be an emotional and/or cognitive dysregulation and may include anxiety and/or anxiety-related states, such as, but not limited to, fear or depression.

[0011] The invention is also directed to administering to a subject that was subjected to the above described methods an anti-anxiety drug or anti-anxiety drug candidate in an anxiety-reducing amount, or subjecting such a subject to anti-anxiety therapy for an anxiety-reducing time-span, and, optionally, monitoring an anxiety-reducing effect of said anti-anxiety drug, anti-anxiety drug candidate or anti-anxiety therapy in said subject. The invention is also directed to detecting the neural activity altered in the amygdala-hippocampal complex by the translational sensory stimulation procedure non-invasively or invasively. Furthermore, the invention is directed to correlating a detected neural activity to a neural activity in another species, for example, by translating/relating the neural activity detected in a non-human animal to the neural activity in a human and vice versa.

[0012] The invention is also directed to a system for the stimulation of an amygdala-hippocampal complex of a subject comprising a generator/transmitter of a translational sensory stimulation procedure (trSP) based on one or more time-series of random sensory pulses, wherein said trSP based on one or more time-series of random sensory pulses is transmitted to a subject and alters the neural activity of the amygdala-hippocampal complex of the subject so that an amygdala-hippocampal complex-dependent physiological function is created, and a non-invasive or invasive neural activity detector, wherein said detector detects an alteration of the neural activity.

[0013] In certain embodiments, the invention is directed to methods for representing the neural activity of the amygdala-hippocampal complex of a subject via functional brain mapping comprising (i) generating and transmitting a translational sensory stimulation procedure based on one or more time-series of random sensory pulses to the subject, which alters the neural activity of the amygdala-hippocampal complex and, (ii) detecting the neural activity altered in the amygdala-hippocampal complex during the transmission of the translational sensory stimulation procedure by emitting a corresponding pulse sequence for the excitation in, and read out of corresponding signals from, the subject and converting the signals into image data.

BRIEF DESCRIPTION OF THE FIGURES

[0014] FIG. 1A) shows a general random sensory pulse sequence. E_i, A_i : i-th pulse with intensity, amplitude or other feature A_i ; Δt_i : time delay between pulse E_i and E_{i+1} ; Δd_i : duration of pulse E_i ; A_i are realizations of random numbers drawn from an arbitrary probability density function $p(x)$ defined on any interval I with $x \in I$; $p(x)$ may be the density function of a Gaussian, Poisson, uniform or other suitable distribution; Δt_i and Δd_i are realizations of random numbers drawn from an arbitrary probability density function $p(x)$ defined on any interval I with $x \in I$ and $x \geq 0$; $p(x)$ may be the density function of a Gaussian, Poisson, uniform or other suitable distribution. Random numbers following a certain probability density function $p(x)$ can be produced numeri-

cally, see for example W.H. Press et. al. "Numerical Recipes" Cambridge University Press 1994.

[0015] FIG. 1B) shows as an example of time-series of random sensory pulses the random presentation of short tones (1 kHz frequency and 40 milliseconds (ms) duration) with an average pulse repetition rate of 5 Hz and a corresponding average repetition time T of $T=1/5 \text{ Hz}=200 \text{ ms}$; a_n , Δd , and b_n are time intervals, and the sum $T=a_n+\Delta d+b_n$ defines one period of 200 ms duration, or 5 Hz; Δd is the duration of the sound pulse of 1 kHz frequency, set to 40 ms. The sound is switched-on and -off smoothly using a sinusoidally increasing and decreasing amplitude ramp with a duration of 3 ms; a_n is a time interval without sound of random duration; a_n is numerically generated for each period n as a realization of a random number derived from a uniform distribution defined within an interval of $[(T/2-\Delta d/2) \cdot (1-\text{var})]$, $(T/2-\Delta d/2) \cdot (1+\text{var})$; var defines the randomness (variation of occurrence) of the sound pulses, and can be set between 0 and 1; $\text{var}=0$ results in a regular order of tones while $\text{var}=1$ gives a random realization of a_n between 0 ms and 160 ms; b_n was calculated via $b_n=200 \text{ ms}-\Delta d-a_n$, using $T=200 \text{ ms}$.

[0016] FIG. 2 shows a time-series of regular and a time-series of random sound pulses with a repetition rate of 5 Hz and 80 Hz, respectively α -axis, time; y -axis, sound level). The sound pulses with the same pulse repetition rate have the same number of pulses per time and the same sound energy.

[0017] FIG. 3 shows an example of a simple block-design stimulation implemented in fMRI. The time-series of random sound pulses generated and transmitted consists of/comprises sound pulses with a repetition rate of 5 Hz, regular sound pulses were applied as well with a repetition rate of 5 Hz.

[0018] FIG. 4 shows blood oxygen level dependent (BOLD) activation by translational sensory stimulation procedure (trSP) through sound pulses in human amygdala-hippocampal complex bilaterally (right>left) in a group of 20 healthy human volunteers (map is shown in white-to-black; scaled in darkness according to gradient black-and-white coding shown on the right side of figure), as determined using functional magnetic resonance imaging (fMRI) in combination with a block-stimulation design as shown in FIG. 3. Statistical evaluation based on a general linear model analysis (p -corrected<0.001). The term " p " is the statistical term of "probability", the lower a p -value, the more statistically significant is the result of an inferential statistical test, typically, p -values below 0.05 are considered statistically significant; the term "corrected" refers to the fact that the image voxel-wise statistical tests have been corrected for the number of voxels in the entire brain slab covered during the fMRI experiment. Parametric statistical map of BOLD response is projected on sagittal (left), coronal (middle) and transversal (right) slices of a standardized brain template (Montreal Neurological Institute [MNI] standard brain; coordinates are in Talairach standard space). Slices are shown in radiological convention (right side of image shows left side of brain and vice versa). The gray-scale gradient illustrates statistical significance.

[0019] FIG. 5 shows induction of the activity-induced immediate-early gene c-Fos in the lateral amygdala of freely moving mice: Left panel, representative mouse brain slice

through lateral amygdala (LA) showing the c-Fos gene product (black stains) after induction of the immediate-early gene c-Fos by trSP through sound pulses. Right panel, results of quantitative analysis of c-Fos induction by trSP (stimulated) compared to a control condition with regularly pulsed sounds in mice (n=7/group; stimulation lasted 4×30 s; *, p<0.05; 2-tailed t-test). The term “p” is as described in **FIG. 4**; the term “t” signifies that a so-called Students-t-test has been employed for inferential statistical comparison between stimulated [exposed to random sound sequences] and control [exposed to regular sound sequences] animals. “t” is quantitative value of how strong the statistical difference between stimulated and control condition was and is used to compute the p-value.

[0020] **FIG. 6A** shows that mice exposed to trSP spent significantly less time in the open arms of an elevated plus maze than when exposed to time-series of regular sound pulses (p<0.05).

[0021] **FIG. 6B** shows that mice avoid the compartment of a maze in which they are exposed to trSP as compared to the compartment in which they hear the regular tones (p<0.005).

[0022] **FIG. 7** shows that trSP increased the “Bias Index”, which indicates an attentional shift towards aversive stimuli, to a level that was previously seen only in high-anxious subjects. Thus, on a behavioral level, in the 17 normal subjects tested, the trSP made normal subjects behave like anxious subjects. (“*” indicates p<0.05).

DEFINITIONS

[0023] As used herein, the term “translational sensory stimulation procedure” (“trSP”) refers to a sensory stimulation procedure based on one or more time-series of random sensory pulses applicable to different kinds of subjects, which can be applied using the same stimulus in the same way e.g. by the same experimental settings equally to different kinds of subjects.

[0024] As used herein, the term “sensory pulses” refers to any kind of pulses e.g. light pulses, tactile pulses, olfactory pulses, gustatory pulses, electric pulses or sound pulses which, if applied to a subject, will cause a physiological stimulus in that subject. As used herein, the term “alteration of neural activity” or “neural activity altered” refers to chemical or electrochemical activity altered by a physiological stimulus caused in that subject by the trSP or directly altered by the trSP.

VARIOUS AND PREFERRED EMBODIMENTS OF THE INVENTION

[0025] The invention is directed to the alteration of neural activity of the amygdala-hippocampal complex of a subject by the trSP according to the stimulation method of the present invention for different purposes such as, but not limited to, the establishment of a model for assessing the effectiveness of anti-anxiety drugs/drug candidates and/or anti-anxiety therapy in humans and non-human animals or the redirection of human or animal behavior via the stimulation method of the present invention. The later can, for example, be used to non-physically deter a subject from entering into certain areas.

[0026] Stimulation according to the present invention can be observed by following the development of e.g. behavior,

anxiety, anxiety-like states, startle response, emotional memory formation or other amygdala-hippocampal complex-dependent physiological functions of the subject while the trSP is generated and transmitted to the subject. The stimulation can be detected by non-invasive means or invasive means. Preferably, the alteration of neural activity is detected by non-invasive means or invasive means. The random sensory pulses generated and transmitted to the subject can be e.g. light pulses, tactile pulses, olfactory pulses, gustatory pulses, electric pulses or sound pulses, preferably random sound pulses are applied. The random sensory pulses are usually generated and transmitted to the subject in a way that they are perceptible by the subject but do not harm the subject. E.g. in case sound pulses are applied to, e.g., a human subject, the range of sound level is usually set between 70 and 100 db (decibel), preferably between 80 and 90 db.

[0027] The trSP based on one or more time-series of random sensory pulses of the present invention may consist of/comprise one or more time-series of random sensory pulses separated by intervals during which no pulses and/or regular sensory pulses are applied as described in **FIG. 3**. Alternatively, the trSP may consist of/comprise a time-series of random sensory pulses, which is generated and transmitted to the subject without intervals of no pulses and/or regular sensory pulses. Whether a time-series of random sensory pulses separated by intervals during which no pulses and/or regular sensory pulses are applied or a time-series of random sensory pulses without intervals of no pulses and/or regular sensory pulses are applied depends on the way the alteration of neural activity of the amygdala-hippocampal complex of the subject is observed and/or detected. In case the development of e.g. behavior, anxiety, anxiety-like states, startle response, emotional memory formation or other amygdala-hippocampal complex-dependent physiological functions of the subject is observed during the trSP is generated and transmitted, a time-series of random sensory pulses without intervals of no pulses and/or regular sensory pulses may be applied. In case the alteration of neural activity is detected by non-invasive means or invasive means, both kind of pulses can be used. However, this is generally not the case if the detection is performed with a method or apparatus which needs control or reference pulses to obtain reliable data such as fMRI, and other functional brain imaging methods such as, but not limited to, positron emission tomography (PET), single photon emission tomography (SPECT) as well as electrophysiological brain mapping methods such as electroencephalography (EEG), magnetoencephalography (MEG) and related methods. If such methods and apparatuses are used, time-series of random sensory pulses separated by intervals during which no pulses and/or regular sensory pulses are preferably applied.

[0028] **FIG. 2** shows, exemplarily for sound pulses, two examples of regular and random pulses with the same pulse repetition rate, the same number of pulses per time and the same pulse energy. The random sensory pulses of a time-series usually have the same physical properties such as the same occurrence of single pulses within a given time, e.g., averaged across one or two seconds and the same pulse energy, e.g., sound energy in case the sensory pulse applied is a sound pulse, as regular sensory pulses.

[0029] A regular time-series of sensory pulses may comprise/consist of a periodic, predictable order of pulses. In

contrast, a random time-series of sensory pulses of the trSP of the present invention may comprise/consist of an order of sensory pulses which is not predictable, i.e., the occurrence of pulses is aleatory and can not be forecasted by the subject exposed to those sensory pulses based on passed order of pulses (the past pulses do not provide sufficient information to predict future pulses). Usually, random time-series of sensory pulses may comprise/consist of an order of pulses generated by separating single sensory pulses by a random time interval Δt , whereby after each sensory pulse, Δt is derived as a realization of a random value according to an arbitrary probability density function $p(\Delta t)$ defined on an interval $\Delta t > 0$. **FIG. 1B** shows a possible realization of a random sensory pulse sequence where the random time interval Δt between pulses is divided into two time periods b_n and a_{n+1} with $\Delta t = b_n + a_{n+1}$. Preferably, a_n is generated numerically for each period as a realization of a random number derived from a uniform distribution defined within an interval of $[(T/2 - \Delta d/2) \cdot (1 - \text{var})]$, $[(T/2 - \Delta d/2) \cdot (1 + \text{var})]$, where T is the mean repetition time of pulses ($T = a_n + \Delta d + b_n$) and var a constant between 0 and 1; b_n is derived via $b_n = T - a_n - \Delta d$; var is a real number that defines the randomness (variation of occurrence) of the sensory pulses, and can be set between 0 and 1, $\text{var} \in [0, 1]$; $\text{var} = 0$ results in a regular order of sensory pulses, while $\text{var} = 1$ gives a maximum random order of sensory pulses. The degree of randomness can be varied by varying var within the formula between 0 and 1. Preferably, the degree of randomness is varied between $\text{var} = 0$ and $\text{var} = 0.9$. The range for the random time interval Δt as defined in **FIG. 1A** is usually $0 < \Delta t \leq 1$ second, preferably $0.001 < \Delta t \leq 0.9$ seconds, $0.01 \leq \Delta t \leq 0.5$ seconds, in particular $0.1 \leq \Delta t \leq 0.3$ seconds. The random time interval Δt does preferably not comprise a sequence of different multiples of Δt , in order to prevent any predictability of the sensory pulse time-series.

[0030] The average pulse repetition rate (as given by $1/(\Delta t + \Delta d)$ in **FIG. 1A** or by $1/T = 1/(a_n + \Delta d + b_n)$ in **FIG. 1B**, $\langle x \rangle$ denotes the expectation value of a random variable x) and can be varied. It is usually between 1 and 100 Hz, preferably between 1 and 10 Hz, more preferably between 2 and 6 Hz. However, with faster pulse repetition rate, the duration of individual pulses must be accordingly shorter.

[0031] The duration Δd of a single sensory pulse can also be a random time interval, whereby Δd is derived after each time interval Δt as a realization of a random value according to an arbitrary probability density function $p(\Delta d)$ defined on an interval $\Delta d > 0$. Δd is usually between 0.001 and 0.5 seconds, preferably between 0.02 and 0.1 seconds. The intensity I of each single pulse can also be random whereby I is derived after each time interval Δt as a realization of a random value according to an arbitrary probability density function $p(I)$ defined on any interval. As probability density functions $p(\Delta t)$, $p(\Delta d)$ and $p(I)$ the density function of a Gaussian, Poisson, uniform or other suitable distribution can be used. Examples for time-series of random intervals of Δt , Δd and I are given in **FIGS. 1A** and **1B**).

[0032] Preferably, the trSP based on more than one time-series of random sensory pulses of the present invention consists of/comprises time-series of random sensory pulses separated by intervals during which no pulses and/or regular sensory pulses are applied. In case time-series of random sensory pulses separated by intervals during which no pulses and/or regular sensory pulses are applied, they are preferably

applied in a so-called block-design fashion. In a block-design fashion, the time-series of random sensory pulses are typically separated by intervals during which no pulses are applied and which are followed by intervals during which regular sensory pulses are applied as shown e.g. in **FIG. 3**. In a block design, a time period of random sensory pulses usually last between 10 seconds and 1 hour, preferably between 20 seconds and 10 minutes, more preferably between 40 seconds and 2 minutes. Usually, the time period applied for time-series of random sensory pulses and for intervals with no pulses and with time-series of regular sensory pulses are balanced, i.e. intervals during which no pulses and/or regular sensory pulses are applied usually last the same time period than the time period for random sensory pulses. The use of a block design allows to directly compare neural activity produced by two different types of stimuli (random and regular sensory pulses) by detecting the general linear contrast between different regressors (or predictors), which is particular useful if fMRI or other means which needs control or reference pulses to obtain reliable data are used as means for detecting the altered neural activity. The statistical evaluation of an effect associated with a given stimulus type is typically based on the so-called General Linear Model (GLM), which is basically a multiple regression analysis and which allows to estimate statistically the contribution of a given stimulus (in GLM used as regressor or predictor) as described in Friston et al. (Hum Brain Mapp 1995; 2:189-210) to the variance in the biological signal, which might be in case of fMRI the BOLD signal and in other means of detection other specific signals.

[0033] The subject is exposed to the translational sensory stimulation procedure of the present invention usually between 1 minute and 24 hours, preferably between 10 minutes and 2 hours more preferably between 20 minutes and 1 hour.

[0034] Means for Generating and Transmitting the Translational Sensory Stimulation Procedure

[0035] Means for generating and transmitting the translational sensory stimulation procedure depend on the kind of sensory pulses applied and comprises usually a sensory output device such as a source to produce the respective pulse time-series like a compact disk player or a tape connected to a sound amplifier, in case the sensory pulses applied are sound pulses, whereby the source is controlled by e.g. a personal computer, or can be controlled by the control unit of the means for detecting the neural activity altered. Means for generating and transmitting sensory pulses to a subject, which can be used to generate and transmit the translational sensory stimulation procedure of the present invention, are known to the persons skilled in the art. The translational sensory stimulation procedure can be transmitted directly from the source to the subject or can be transmitted by an appropriate auxiliary device. In case of light pulses, transmission of light occurs usually directly to the light sensitive parts of the subject e.g. the eyes of a human or an animal are directly exposed to the light source. In case of tactile pulses, electric pulses or sound pulses usually an appropriate auxiliary device such as devices, which are in contact with the surface of the subject, electrodes or headphones are applied.

[0036] Amygdala-Hippocampal Complex

[0037] The "amygdala-hippocampal complex" referred to in the present invention encompasses the amygdala plus the

anterior hippocampus. The amygdala plus the anterior hippocampus includes a group of neural nuclei comprising the so-called amygdaloid complex and the anterior hippocampus. The anterior hippocampus comprises the pes hippocampus and the anterior portion of the subiculum as defined in Bohbot et al. (*Neuropsychologia* 1998; 36:1217-1238). The amygdaloid complex comprises the lateral, basal, accessory basal, and centromedial nuclei as described in Sah et al. (*Ann NY Acad Sci* 2003; 985:67-77). The amygdaloid complex is preferably stimulated by the stimulation procedure of the present invention, whereby the lateral part is particularly stimulated. In case the subject exposed is a human, the term "amygdala-hippocampal complex" referred to in the present invention encompasses said amygdala plus the anterior hippocampus. In case the subject exposed is an animal, the term amygdala-hippocampal complex usually encompasses the amygdala and the anterior portion of the hippocampus, which are tightly interconnected as described in e.g. Pare et al. (*J Neurosci* 1996; 16:3334-50). The amygdala-hippocampal complex as a whole as well as part or parts of the complex can be stimulated both in vivo and in vitro e.g. in acute brain slice preparations or in a cell culture of amygdala cells or in in vitro preparations of amygdala-hippocampal complex cells or cellular networks. Normally in in vitro preparations the stimuli used are electric pulses suitable to stimulate in vitro cell preparations.

[0038] Subject

[0039] Subjects, which can be exposed to the stimulation procedure of the present invention, are living beings, which have developed an amygdala-hippocampal complex e.g. humans and non-human animals ("animals"), usually, humans and animals are exposed. The stimulation procedure can be applied to healthy humans, humans with a specific genetic background, which is known to be a risk factor for mental-health conditions or patients with mental health problems encompassing affective and/or emotional and/or cognitive dysregulation such as e.g. patients with mood disorders, anxiety disorders, schizophrenia, personality disorders, addiction and related disorders. Animals usually exposed to the stimulation procedure are mammals like monkeys or rodents like mice, rats or rabbits and are usually laboratory animals. The animals might be healthy or might have developed behaviors, which can be used as model of mental health conditions naturally or by laboratory treatment. One might use animals showing similarities to affective/emotional dysregulation state conditions e.g. different kind of strains with altered fear-related behavior or altered social behavior, or animals with specific genetic background e.g. knock-out or transgenic animals, or animals treated behaviorally to show affective-like or emotionally dysregulated behavior patterns (e.g. by early separation from mother, by induction of learned helplessness), or animals treated pharmacologically to exhibit altered behavior and/or physiology modelling mental health problems in humans or animals with brain lesions.

[0040] The stimulation procedure of the present invention can be applied using the same stimulus in the same way, e.g., by the same experimental settings equally to all subjects independent of the kind of subject exposed. Therefore, the responsiveness of the application of the stimulation procedure in different subjects can be directly compared in a truly translational approach.

[0041] Neural Activity

[0042] The alteration of the neural activity in the amygdala-hippocampal complex by the trSP can be an increase or a decrease of the neural activity, or the neural activity can be one or more times increased and thereafter be decreased or vice versa over the time-series the subject is exposed to the stimulation procedure of the present invention. In case time-series of random and regular sensory pulses are applied the alteration caused by the time-series of random sensory pulses can be a disproportional increase (as compared to the regular stimulation procedure). Usually, the neural activity in the amygdala-hippocampal complex stimulated by the trSP is increased.

[0043] In case the neural activity altered in amygdala-hippocampal complex by the translational sensory stimulation procedure is detected by non-invasive means or invasive means, preferably, non-invasive means are used. Non-invasive means, which can be applied in the present invention are known to the person skilled in the art and are usually means for functional brain mapping selected from the group comprising the functional magnetic resonance imaging (fMRI) and related magnetic resonance imaging-based techniques, electroencephalography (EEG), magnetoencephalography (MEG), positron emission tomography (PET), infrared imaging (IR) or single photon emission computer tomography (SPECT). Related magnetic resonance imaging-based techniques which can be used are as described by Xiong et al. (*Hum Brain Mapp* 2003; 20:41-9) and Buxton (*Introduction to Functional Magnetic Resonance Imaging: Principles and Techniques*. Cambridge, N.Y., Cambridge University Press, 2002). Preferably fMRI and related magnetic resonance imaging-based techniques are used, more preferably fMRI is used. Detection of the neural activity in the brain of a subject stimulated by the translational sensory stimulation procedure of the present invention by fMRI shows that the trSP alters the neural activity specifically in the amygdala-hippocampal complex of the subject as shown in FIG. 4.

[0044] The respective non-invasive means used in carrying out the present invention are known to the skilled person and are commercially available. In case fMRI is used, the neural activity within the amygdala-hippocampal complex of the subject exposed to the translational sensory stimulation procedure is usually detected by measuring e.g. blood oxygen level-dependent (BOLD) signals, regional cerebral blood flow (rCBF), regional cerebral blood volume (rCBV), regional magnetic fields, or regional electric signals. Preferably, blood oxygen level-dependent (BOLD) signals are measured, however, future developments in MRI-related technologies will enable detecting other signal sources such as regional magnetic fields, and regional electric or magnetic signals, as described e.g. in Xiong et al. (*Hum Brain Mapp* 2003; 20:41-9).

[0045] In case non-invasive means are applied, the means for generating and/or transmitting the translational sensory stimulation procedure are usually connected and controlled by a control unit of the respective non-invasive means used e.g. MRI-compatible audio, light, tactile, gustatory, olfactory, sound or electric pulse transmission systems. The obtained signal, however, does not have to be chronologically correlated with the stimulation procedure generated and transmitted in order to detect altered neural activity in the amygdala-hippocampal complex.

[0046] In case invasive means are used, the subject is usually equipped with intracerebral electrodes in specific part of the amygdala-hippocampal complex, e.g., intracerebral electrodes allowing for single cell recording, or with suitable intracerebral imaging probes like infrared probes or calcium imaging probes or the subject is sacrificed within a short period of time after the subject was exposed to the translational sensory stimulation procedure of the present invention and the amygdala-hippocampal complex or a part of the amygdala-hippocampal complex or cells thereof are analyzed for altered neural activity. The neural activity altered can be detected by e.g. measuring the induction of genes specific for the stimulation of the amygdala-hippocampal complex like the immediate early gene c-Fos or other suitable gene products such as zif268, CREB or Erk-1/2 within the amygdala-hippocampal complex by using usual molecular biological techniques. Preferably, the induction of genes specific for the stimulation of the amygdala-hippocampal complex, particularly the induction of the c-Fos gene product, is measured.

[0047] The neural activity altered in the amygdala by the translational sensory stimulation procedure of the present invention is normally sustained for a period of at least 15 seconds, preferably at least 60 seconds, more preferably at least 5 minutes, in particular at least 20 minutes up to the whole time the subject is exposed to the translational sensory stimulation procedure of the present invention. The sustained period might be dependent of the kind of subject exposed to the translational random stimulation procedure. The neural activity altered by the translational sensory stimulation procedure of the present invention is non-habituating, i.e. every exposition of multiple expositions of the subject to the time-series of random sensory pulses alters de novo neural activity in the amygdala-hippocampal complex of the subject exposed.

[0048] The system for the stimulation of the amygdala-hippocampal complex of a subject comprising i) means for generating and transmitting a translational sensory stimulation procedure based on one or more time-series of random sensory pulses to said subject, which alters the neural activity of said amygdala-hippocampal complex, and ii) non-invasive or invasive means for detecting the neural activity altered in said amygdala-hippocampal complex by said translational random stimulation procedure comprises the means for generating and transmitting a translational random procedure and the means for detecting the neural activity altered in said amygdala-hippocampal complex by said translational sensory stimulation procedure as described above. The translational sensory stimulation procedure is generated and transmitted to a subject as described above. The subject exposed is the same kind of subjects as described above.

[0049] The present invention also provides a method for the representation of the neural activity of the amygdala-hippocampal complex of a subject by means of functional brain mapping, which can be applied translationally to different kind of subjects thereby allowing for a direct and simple comparison of the representation received for different subjects.

[0050] The neural activity of the amygdala-hippocampal complex of a subject is represented by means for functional brain mapping by the following method comprising:

[0051] i) generating and transmitting a translational sensory stimulation procedure based on one or more time-series of random sensory pulses to said subject, which alters the neural activity of said amygdala-hippocampal complex,

[0052] ii) detecting the neural activity altered in said amygdala-hippocampal complex during the transmission of said translational sensory stimulation procedure by emitting a corresponding pulse sequence for the excitation in, and read out of corresponding signals from, said subject and converting said signals into image data.

[0053] Means for functional brain mapping are usually selected from the group comprising the functional magnetic resonance imaging (fMRI) and related magnetic resonance imaging-based techniques, electroencephalography (EEG), magnetoencephalography (MEG), positron emission tomography (PET), infrared imaging (IR), single photon emission computer tomography (SPECT).

[0054] Also encompassed by the present invention is a device for the representation of the neural activity of the amygdala-hippocampal complex of a subject comprising:

[0055] i) means for generating and transmitting a translational sensory stimulation procedure based on one or more time-series of random sensory pulses to said subject which alters the neural activity of said amygdala-hippocampal complex,

[0056] ii) means for detecting the neural activity altered in said amygdala-hippocampal complex during the transmission of said translational sensory stimulation procedure by emitting a corresponding pulse sequence for the excitation in, and read out of corresponding signals from, said subject and converting said signals into image data.

[0057] For the detection of the neural activity of the amygdala-hippocampal complex of the subject during the transmission of said translational sensory stimulation procedure, the subject is positioned in a usual device for functional brain mapping selected from the group mentioned above with standard equipment known to the person skilled in the art. Such devices and the way how to use them is described in Toga A. and Mazziotta J. [editors], *Brain Mapping: The Methods*, Elsevier-Academic Press, Amsterdam NL, 2002, and Moonen & Bandettini [editors]: *Functional MRI*. Berlin, Heidelberg, Springer-Verlag, 2000. Preferably, fMRI is used as the functional brain mapping method for the representation of the neural activity of the amygdala-hippocampal complex.

[0058] Further encompassed by the present invention is the use of the methods of the present invention in the translational study of affective or emotional dysregulation of a subject.

[0059] Affective or emotional dysregulations, which can usually be studied with the methods of the present invention are e.g. affective (depression) and anxiety-related disorders as well as related disorders such as schizophrenia, personality disorder, addiction and other mental health conditions as well as dysregulations of emotional memory formation, fear processing, emotional recognition, social functions,

associative learning mechanisms, and other physiological functions related to emotional regulation and dysregulation.

[0060] Consequently, the present invention can be used in characterizing clinically and preclinically the above mentioned conditions both in terms of cross-sectional and longitudinal characterization, e.g., in terms of studying neural underpinnings of such diseases ("pathophysiological characterization", such as described e.g. by Phillips et al. (*Biol Psychiatry* 2003; 54:515-28)), of studying neural underpinnings of pharmacological and other treatment effects ("therapy monitoring", such as described e.g. by Davidson et al. (*Am J Psychiatry* 2003; 160:64-75)), or of studying neural underpinnings of risk factors for such diseases ("endophenotyping", such as described e.g. by Hariri and Weinberger (*Br Med Bull* 2003; 65:259-70)). In particular, the effectiveness of drugs, drug candidates and therapies that seek to alleviate and/or treat emotional dysregulations can be tested.

EXAMPLES

Example 1

[0061] Persistent Alteration of Neural Activity in the Amygdala-Hippocampal Complex of Healthy Humans

[0062] 20 healthy volunteers were studied in the fMRI using auditory stimulation. Auditory stimuli consisted of 60-s blocks with random and regular sound pulse sequences (as shown in **FIG. 3**). Sounds were pure tones with a carrier frequency 1 kHz and an amplitude envelope (100% modulation) resulting in a 5 Hz-repetition rate of sound pulses with a duration of 20 ms (random with $\text{var}=0.6$ in the random-stimulus-condition, regular in the regular-stimulus-condition) with an average duty cycle of 50%. Sound pressure levels were set to 90 dB in all conditions. The sound energy delivered to the subjects was the same for random and regular sound pulse sequences. Auditory stimuli were presented to the subjects bilaterally using magnetic resonance imaging-compatible sound delivery system (Commander XG, www.mrvideo.com). In order to map out the time-course of activation across the 60-s duration of the stimulus epoch, image volumes were acquired with brief inter-volume intervals of 2.14 s. Image acquisition produced a banking background noise of approximately 100 dB, however, the noise reduction by the headphones of approximately 30 dB and the spectral composition of the scanner noise enabled a clear perception of experimental stimuli.

[0063] Random and regular stimulus sequences were implemented in a block-design alternating between stimulation (60 s) and resting (30 s) conditions as shown in **FIG. 3**. Subjects were instructed to passively listen to the sound stimuli, however they were not asked to carry out any output tasks or to make judgments about the stimuli ('passive listening' without explicit rating or any task other than listening, such as e.g. in Critchley et al, (*Hum Brain Mapp* 2000; 9:93-105). Magnetic resonance images were acquired on a 1.5 T Symphony scanner equipped with a circularly polarized head coil. Anatomical T_1 -weighted volumes were obtained with a three-dimensional magnetization prepared rapid acquisition gradient echo sequence at a voxel size of 1 mm^3 (repetition time TR, 9.7 ms; echo-time TE, 4 ms). Functional T_2^* -weighted images were acquired using gradient-recalled echo-planar imaging (TE, 54 ms; TR, 2675

ms; inter-slice time, 107 ms), which is a standard fMRI sequence to detect changes in regional blood oxygenation level-dependent (BOLD) signal which is accepted to index neural activity (see e.g. Logothetis et al., *Nature* 2001; 412:150-7). A series of 865 functional near-whole-brain volumes consisting of 20 contiguous oblique slices 4 mm thick (field of view, $180 \times 180 \text{ mm}^2$; matrix, 64×64 pixels) were acquired. The first 8 volumes were discarded to obtain steady state regarding longitudinal magnetization and scanner-induced auditory excitation.

[0064] Images were postprocessed using BrainVoyager (www.braininnovation.com). The functional time-series were corrected for slice-acquisition time through sinc interpolation, realigned with their corresponding T_1 -volumes, warped into Talairach-space, resampled into 3-mm isotropic voxels, motion-corrected using Levenberg-Marquart's least square fit for six spatial parameters, corrected voxelwise for linear drifts, and smoothed using a 6-mm full-width at half-maximum gaussian kernel. Condition-specific stimulus boxcar functions were convolved with a gamma-kernel to model the hemodynamic response behavior. The cortical areas responding to auditory stimulation were identified by applying general linear model analyses to z-transformed time-series in each image voxel and used random and regular sound sequence stimulus conditions as explanatory variables. Stimulus-specific effects were calculated using the general linear model (GLM) contrast. These contrasts were voxel-wise Bonferroni-corrected ($p < 0.05$). Statistical maps were superimposed on anatomical sections and inflated cortical surfaces of the standardized Montreal Neurological Institute T_1 -weighted brain template (www.bic.mni.mcgill.ca).

[0065] Time-series of random and regular sound pulses produced blood oxygen level-dependent (BOLD) signal change in auditory cortex; however, in auditory cortex the BOLD responses to the two stimulus types were not statistically significantly different. In comparing the brain activity induced by time-series of random vs. regular sound pulse stimuli, a significant general linear contrast bilaterally in the amygdala and the amygdala-hippocampal complex was found, whereby the differential contrast was stronger in the right compared to the left amygdala and amygdala-hippocampal complex (**FIG. 4**).

Example 2

[0066] Induction of c-Fos in the Amygdala of Freely Moving Mice

[0067] Adult male C57 Bl/6 mice (RCC) were housed individually in Plexiglas cages and were maintained on a free feeding regimen with a 12/12 h light/dark schedule. All studies took place during the light portion of the cycle.

[0068] Experimental Design: Before training, mice were habituated to being handled during 4 days (5 minutes per day), transported from the colony room to the experimental chamber and familiarized with a neutral context consisting of a square transparent plexiglas box (27 cm side $\times$ 72 cm high) with a grid floor made of stainless steel rods. The whole system was placed inside a sound attenuating and temperature-regulated Plexiglas cubicle. A speaker was positioned on top of the square transparent box. This context was cleaned with 70% ethanol before and after each animal. On the training day, mice were divided into 3 groups. Mice

of the Regular group (REG group, $n=6$ mice) were submitted to 4 presentations (inter-trial interval: 30-240 s) of a series of 5 kHz bips (duration $\Delta d=20$ ms) regularly distributed at 5 Hz for 30 s (constant $a_n=b_n=90$ ms). Mice of the Random group (RAND group, $n=7$ mice) were submitted to 4 presentations (inter-trial interval: 30-240 s) of a series of 5 kHz bips (duration $\Delta d=20$ ms) randomly distributed at an average frequency of 5 Hz for 30 s ($\text{var}=0.8$, a_n randomly uniformly distributed within an interval of $[(100-10)(1-\text{var})]$, $(100-10)(1+\text{var})$ ms= $[18,162]$ ms, and $b_n=200$ ms- $a_n-\Delta d$ as shown in FIG. 1B).

[0069] Immunohistochemistry: Mice were deeply anesthetized using isoflurane (5% in oxygen.) 2 hrs after the last presentation of an auditory stimulus and perfused transcardially with ice-cold solutions of 9 g/l NaCl followed by 4% of paraformaldehyde in phosphate buffer (PB; pH 7.4). After post-fixation overnight in the same fixative at 4° C., coronal sections (50 μ m) were cut on a vibratome (Leica) and collected in PB. Free-floating sections were rinsed in phosphate buffer saline (PBS) and pretreated with 0.3% H_2O_2 in PBS to reduce endogenous peroxidase activity. After four rinses, sections were incubated in a blocking solution (3% bovine serum albumin (BSA)/0.2% Triton X100) for 1 hour (hr) at room temperature (RT). Then, they were incubated in primary polyclonal rabbit anti-c-Fos (Oncogene Research Products; 1:20000 dilution) antibody in the blocking solution overnight at RT. Subsequently, sections were washed with PBS and incubated for 2 hrs at RT with biotinylated goat anti-rabbit IgG (Vector Laboratory; 1:400 in PBS) followed by 2 hrs at RT in the avidin-biotin peroxidase complex (Vectastain Elite kit, Vector Laboratories). Sections were rinsed in PBS and then PB. The peroxidase reaction end-product was visualized by incubating sections in 0.1 M PB containing 3,3' diaminobenzidine tetrahydrochloride (DAB, 0.037%) as chromogen and hydrogen peroxide (0.015%) for 20 min. Finally, immunolabeled sections were washed in PB, mounted on gelatin-coated slides, dehydrated and coverslipped.

[0070] Data analysis: The quantification of c-Fos positive cells was carried out at a $\times 10$ magnification, which yielded a field of view of $849 \times 637 \mu\text{m}$. At least three serial sections were digitized and analyzed using a computerized image analysis system (Biocom, Visiolab 2000, V4.50). The number of nuclei was quantified in the following areas of interest [according to Franklin and Paxinos (1996); - signifies posterior to bregma]: amygdala (BL and LA, bregma -1.3 to -1.9 mm). The counting was performed in an area of the same shape and size for each brain region. Nuclei were counted individually and expressed as number of c-Fos positive nuclei per mm^2 . At all stages, the experimenter was blind to the experimental groupings. Statistical analysis of immunocytochemical studies were performed by unpaired two-tailed student's t-test at the $p < 0.05$ level of significance. Data are presented as group means $\pm$ SEM (standard error of mean). FIG. 5 (left) shows a slice through the lateral amygdala of a mouse that has been stimulated (4 $\times$ 30 s) using the trSP of the present invention. Results of quantitative analysis of c-Fos induction by the trSP of the present invention (stimulated) compared to a control condition with regularly pulsed sounds indicate alteration of the neural activity of the lateral amygdala by the trSP.

Example 3

[0071] Persistent Alteration of Neural Activity in the Lateral Amygdala and Closely Connected Portions of the Hippocampus of Freely Moving Mice

[0072] Data from electrophysiological trials using extracellular single unit recordings in lateral amygdala (LA) and closely connected portions of the hippocampus of freely moving mice show that stimulation with random sound sequences (trSP), compared to corresponding regular sound sequences, increases neural activity in LA. Single unit recordings were performed according to standard procedures used in freely moving rats (as described e.g. by Quirk et al. (Neuron 1997; 19:613-24) and Neugebauer and Li. (J Neurophysiol 2003; 89:716-27)).

Example 4

[0073] Behavioral Consequences of trSP in Mice as Indicated by the Elevated Plus-Maze and the Place-Preference Paradigms

[0074] Elevated Plus-Maze: In the field of anxiety, the elevated plus-maze is one of the most widely used animal models (see Lister, Psychopharmacology 1987; 92:180-185; Korte and De Boer, Eur. J. Pharmacol. 2003; 463:163-175). The test involves placing a naïve mouse in the center of an elevated plus-maze with two open and two enclosed arms, and allowing it to freely explore. It has been shown that the reluctance of the animal to explore the open arms of the maze is caused by fear of open spaces. Anxiolytic compounds increase, whereas anxiogenic compounds decrease the percentage of time spent on open arms (see, Pellow et al., J. Neurosci. Methods 1985; 14: 149-167; Cole et al., Psychopharmacology 1995; 121:118-126). The basolateral nucleus of the amygdala (BLA) has been shown to be important for the consolidation of anxiety in the elevated plus-maze (File et al., Neuropsychopharmacology 1998; 19:397-405), and manipulations of the BLA can increase anxiety-like behavior on the plus-maze (see, Belcheva et al., Neuropharmacology 1994; 33:995-1002; Wallace et al., Biol. Psychiatry 2004; 56:151-160; Vyas and Chattarji, Behav Neurosci. 2004; 118: 1450-1454).

[0075] It was investigated whether exposing mice to trSP would induce an anxiety-like behavior (i.e., a reduction of the time the animal spends on the open arms of the elevated plus maze). The maze had two open arms and two closed arms (10 $\times$ 50 cm) perpendicular to each other, and elevated 50 cm from the floor. The walls of the closed arms were 15 cm high with no ledges in the open arms. The maze was cleaned with water between each animal. Mice were individually placed in the center of the plus maze facing an open arm for a 2 min habituation period. Immediately following habituation, trSP or regular tones (20 ms bips at 5 kHz, delivered at an average frequency of 3 Hz, 85 dB) were delivered during 5 min each. The presentation of the tones was counterbalanced for half of the mice tested. The position of the mouse in the maze was continuously monitored during the session using a video-tracking system. The total time spent in closed and open arms was then calculated during trSP and regular stimulation.

[0076] It was found, that mice exposed to trSP spent significantly less time on the open arms of the elevated plus-maze ($n=10$; $p < 0.05$; FIG. 6A). Thus, trSP induces behavioral changes commonly associated with anxiety.

[0077] Place-Aversion: In principle, a decrease in the time spent in the open arm of the elevated plus-maze could also be explained by a trSP-induced increase in attention of open spaces or of height. To address the question of whether trSP has an inherent aversive property, it was tested if mice would avoid a neutral context paired with trSP as compared to a neutral context paired with regular auditory stimulation.

[0078] The place aversion apparatus consisted of a grey Plexiglas square chamber (38.5×25×25 cm) and a grey Plexiglas circular chamber (35 cm diameter), both of which were connected to one another by a small, grey square-shaped Plexiglass alleyway (10×10×25 cm). Geometric cues were placed on the wall of the circular chamber only. After each mouse, the square and circular chambers were cleaned with a 1% acetic acid and 70% ethanol solutions, respectively. The entire experiment lasted 4 days during which the behavior of the mice was continuously monitored using a video-tracking system. The first day, each mouse was placed in front of a wall in the central alleyway for two sessions of 15 min during which they could freely explore the two chambers. At the end of this phase, the compartment in which the mouse spent most of its time was designated as the preferred compartment. Mice were then divided into two groups and placed in the apparatus for a 15 min session during the next three days. For the first group, trSP (20 ms bips at 5 kHz, delivered at 3 Hz in average, 85 dB) was presented each time the mouse entered its preferred compartment whereas a regular tone (20 ms bips 5 kHz, delivered at 3 Hz, 85 dB) was systematically delivered when the mouse entered the non-preferred compartment. The total time spent in each compartment was then calculated and compared to the pre-stimulation baseline values.

[0079] Exposing mice to trSP in their preferred compartment induced a significant reduction in the time they spent in this compartment (n=4; p<0.01; FIG. 6B). This effect can not be explained by a trSP-induced increase in attention, but rather indicates that trSP is intrinsically aversive to mice thereby inducing anxiety-like behavior.

Example 5

[0080] Behavioral Consequence of trSP in Healthy Human Subjects Indicated by the Visual Dot Probe Paradigm

[0081] The Visual Dot Probe paradigm is an indicator for spatial shift of attention towards emotionally aversive stimuli. A positive "Bias Index" in this paradigm, indicating an attentional shift, has been found in patients with anxiety disorders (Mogg et al., *Handbook of Cognition and Emotion*, ed. T. Dalgleish & M. Power 1999; pp. 145-170) and in high-anxious normal subjects, but not in low-anxious subjects (Mogg et al., *Behavioral Research and Therapy* 1997; 35:297-303). Thus, the Visual Dot Probe paradigm is a suitable probe to examine whether the application of trSP makes healthy human subjects behaving like anxious human subjects, or, in other words, to examine the behavioral consequence of stimulation with trSP and the neural activation in the amygdala-hippocampal complex.

[0082] The influence of trSP on the attentional shift towards aversive stimuli was investigated. In a within-subjects design with three conditions, 17 healthy subjects listened to trSP (random sound pulses, 5 Hz repetition rate, as shown in FIG. 2), control sounds (regular sound pulses, 5 Hz repetition rate, as shown in FIG. 2), and no sound

(silence) in randomized order. The Visual Dot Probe Paradigm was conducted with 16 relevant trials and 48 distraction trials in each condition. In each relevant trial, a neutral and an aversive word were presented for 50 ms, which were matched for syllable and character count. A dot appeared immediately afterwards, either in place of the neutral (discordant) or of the aversive word (concordant). In a Go-NoGo-task, subjects responded to the dot by pressing a key and the reaction time was measured. A "Bias Index" (c.f. FIG. 7) was calculated for these 17 health subjects as difference between concordant and discordant trials.

[0083] It was found that the "Bias Index" did not deviate from zero in a no-sound (silent) and control-sound (regular sounds) condition. In other words, this finding indicated that control sound did not alter the subjects' behavior towards "anxious" behavior. During trSP, however, the "Bias Index" was 10 ms, which was statistically significantly different from the silent and regular control sound conditions. Notably, there was no general change of reaction times towards neutral or aversive words during trSP.

[0084] In summary, trSP elicited a spatial shift of attention towards aversive stimuli. Such a phenomenon, as quantified by the size of the "Bias Index" is typically seen only in high-anxious subjects (Mogg et al., *Behavioral Research and Therapy* 1997; 35:297-303). Since no overall reaction time change was found during trSP, the specificity of the present findings is supported because they can not be explained by an unspecific general change of arousal or vigilance. In contrary, vigilance and attention was specifically shifted, like in high-anxious subjects, towards aversive stimuli.

What is claimed is:

1. A method for stimulating an amygdala-hippocampal complex of a subject comprising

generating and transmitting a translational sensory stimulation procedure (trSP) based on one or more time-series of random sensory pulses to said subject, wherein said trSP alters the neural activity of said amygdala-hippocampal complex of said subject so that an amygdala-hippocampal complex-dependent physiological function is created.

2. The method of claim 1, wherein said amygdala-hippocampal complex-dependent physiological function is an emotional and/or cognitive dysregulation.

3. The method of claim 1, wherein said amygdala-hippocampal complex-dependent physiological function is anxiety or an anxiety-like state.

4. The method of claim 3 further comprising

administering to said subject an anti-anxiety drug or anti-anxiety drug candidate in an anxiety reducing amount, or subjecting said subject to anti-anxiety therapy for an anxiety reducing time-span, and,

optionally, monitoring an anxiety reducing effect of said anti-anxiety drug, anti-anxiety drug candidate or anti-anxiety therapy in said subject.

5. The method of claim 1, further comprising detecting the neural activity altered in said amygdala-hippocampal complex by said translational sensory stimulation procedure non-invasively or invasively.

6. The method of claim 1, wherein said subject is a non-human animal and wherein said method further comprises translating said detected neural activity to a neural

activity in a human or, wherein said subject is a human and wherein said method further comprises translating said detected neural activity to a neural activity in a non-human animal.

7. The method of claim 1, wherein the random sensory pulses are random sound pulses.

8. The method of claim 1, wherein the time-series of random sensory pulses comprise an order of pulses generated by separating single sensory pulses by a random time interval Δt , whereby after each sensory pulse, Δt is derived as a realization of a random value according to an arbitrary probability density function $p(\Delta t)$ defined on an interval $\Delta t > 0$.

9. The method of claim 1, wherein said translational sensory stimulation procedure comprises one or more time-series of random sensory pulses separated by intervals during which no pulses and/or regular sensory pulses are generated.

10. The method of claim 9, wherein said time-series of random sensory pulses separated by intervals during which no pulses and/or regular sensory pulses are generated in a block-design fashion.

11. The method of claim 5, wherein the neural activity is detected by functional magnetic resonance imaging (fMRI) or related magnetic resonance imaging-based techniques, electroencephalography (EEG), magnetoencephalography (MEG), positron emission tomography (PET), infrared imaging (IR), or single photon emission computer tomography (SPECT).

12. The method of claim 1, wherein the altered neural activity in said amygdala-hippocampal complex is sustained for a period of at least about 15 seconds.

13. A system for the stimulation of an amygdala-hippocampal complex of a subject comprising:

- i) a generator/transmitter of a translational sensory stimulation procedure (trSP) based on one or more time-series of random sensory pulses to said subject, wherein said trSP based on random sensory pulses is transmitted to said subject and alters the neural activity of said amygdala-hippocampal complex of said subject so that an amygdala-hippocampal complex-dependent physiological function is created, and
- ii) a non-invasive or invasive neural activity detector, wherein said detector detects the alteration of said neural activity.

14. The system of claim 13, wherein the random sensory pulses are random sound pulses.

15. The system of claim 13, wherein the random sensory pulses comprise an order of pulses generated by separating single sensory pulses by a random time interval Δt , whereby after each sensory pulse, Δt is derived as a realization of a random value according to an arbitrary probability density function $p(\Delta t)$ defined on an interval $\Delta t > 0$.

16. The system of claim 13, wherein the neural activity detector is based on functional magnetic resonance imaging (fMRI) and related magnetic resonance imaging-based techniques, electroencephalography (EEG), magnetoencephalography (MEG), positron emission tomography (PET), infrared imaging (IR), or single photon emission computer tomography (SPECT).

17. A method for representing the neural activity of an amygdala-hippocampal complex of a subject via functional brain mapping comprising:

- i) generating and transmitting a translational sensory stimulation procedure based on one or more time-series of random sensory pulses to said subject, which alters the neural activity of said amygdala-hippocampal complex,
- ii) detecting the neural activity altered in said amygdala-hippocampal complex during the transmission of said translational sensory stimulation procedure by emitting a corresponding pulse sequence for the excitation in, and read out of corresponding signals from, said subject and converting said signals into image data.

18. The method of claim 17, wherein the random sensory pulses comprise an order of pulses generated by separating single sensory pulses by a random time interval Δt , whereby after each sensory pulse, Δt is derived as a realization of a random value according to an arbitrary probability density function $p(\Delta t)$ defined on an interval $\Delta t > 0$.

19. The method of claim 17, wherein the neural activity is detected by detecting the blood oxygen level-dependent (BOLD) signal with functional magnetic resonance imaging (fMRI) in said subject.

20. A device for representing the neural activity of an amygdala-hippocampal complex of a subject comprising:

- i) a generator/transmitter of a translational sensory stimulation procedure (trSP) based on one or more time-series of random sensory pulses to said subject, wherein said trSP is transmitted to said subject and alters the neural activity of said amygdala-hippocampal complex in said subject so that an amygdala-hippocampal complex-dependent physiological function is created, and
- ii) a neural activity detector, wherein said detector detects the alteration is said neural activity in said amygdala-hippocampal complex during transmission of said trSP by emitting a corresponding pulse sequence for the excitation in, and read out of corresponding signals from, said subject and converting said signals into image data.

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摘要(译)

本发明涉及基于一个或多个随机感觉脉冲的时间序列通过平移感觉刺激程序刺激受试者的杏仁核 - 海马复合体的方法和系统。此外，它涉及表示受试者的杏仁核 - 海马复合体的神经活动的方法。

Figure 1

