Eur Arch Psychiatry Clin Neurosci (2008) 258:226–238 DOI 10.1007/s00406-007-0783-6

ORIGINAL PAPER

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Neuropsychiatry

An old discipline in a new gestalt bridging biological psychiatry, neuropsychology, and cognitive neurology

Received: 24 July 2007 / Accepted: 30 October 2007 / Published online: 23 February 2008

Abstract The recent developments of psychiatry getting better insight into the biological basis of psychiatric disorders questions the old division between psychiatry and neurology. The present paper focus on the concept of neuropsychiatry, its historical antecedents and closely associated disciplines like biological psychiatry, behavioral neurology and neuropsychology. A special emphasis is put on the question of function and localization; the suggestions are made that the concept of neuronal integration may bridge the often discussed gap between localization and holism in the relation between function and brain regions. Examples of different mechanisms of neuronal integration are discussed and applied to specific neuropsychiatric disorders. It is concluded that the concept of neuronal integration may offer an appropriate conceptual tool to establish the concept of neuropsychiatry in a new and meaningful gestalt at the interface between biological psychiatry, neuropsychology and cognitive neurology.

Introduction: the concept of "Neuropsychiatry"

A clinician taking care of a patient suffering from Parkinson's disease does not have to treat motor symptoms alone (tremor, akinesia, and rigor), which belong to the field of neurology, but beyond he also has do diagnose and treat affective (e.g., depressions) or cognitive symptoms (e.g., bradyphrenia, retardation of thinking), which belong to the field of psychiatry. However, it is quite unlikely that he will meet all requirements of both fields because either he is a neurologist or a psychiatrist, and he therefore has learned different ways of thinking and different methods. This reflects the paradox situation in contemporary relationship between neurology and psychiatry: On one hand, neurology and psychiatry are regarded as two different disciplines with different content concerning methodology, diseases, diagnostics and therapy. On the other hand, the boundaries of separation between both disciplines melt away by applying neurological methodology and diagnostics in psychiatric diseases (CT, Spect, and PET) as well as by the interest of neurology in complex mental functions and psychiatric symptoms in neurological diseases. Particularly in the Anglo-American region this resulted in the foundation of the discipline of "neuropsychiatry": "Although half a century ago neurology and psychiatry seemed to be diverging from a common purpose and sanding as two stools apart, these recent advances have not only seen the stools bridged by a plank, but the whole structure has come gradually to resemble a bench, which for some seems quite comfortable. The last decade has seen not only an exponential growth of knowledge in the field of the neurosciences, but also a resolution of some interdisciplinary rivalry, and laid the foundations of neuropsychiatry for at least the rest of this century." [117] (Tables 1, 2)

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Neurology, psychiatry and neuropsychiatry

Historic development of the separation of neurology and psychiatry

Neurology as an independent discipline has developed at the beginning of the nineteenth century when Parkinson's disease and Multiple sclerosis were defined as neural diseases [97] (see also Ref. [4]). Following advances in anatomy and pathology in the

Table 1 Historic comparison between neurology and psychiatry

Neurology	Psychiatry
Diseases of the brain's anatomic structure	Diseases of the mind
Structural diseases	Functional diseases
Localization in the brain	Non-localization in the brain
Clinical–pathological correlations	No clinical–pathological correlations
Distinct syndromes and disease entities, demarcated by neuroanatomical findings	Unclear disease entities, demarcated by clinical observation
Organic brain	Psychological brain

nineteenth century correlations between the clinical appearance and the pathological–anatomical substrate became possible to an increasing degree; this has been successful in numerous neurological diseases and symptoms (e.g., aphasia) and consequently established the field of neurology as an independent discipline of medicine. On the contrary clinical–pathological correlations in psychiatry did not show significant success, which strengthened the separation of medicine/neurology on the one hand and psychiatry on the other hand. The previously apparent connection between psychiatry and philosophy/humanities [97], the letter dealing with mental states as implicated in psychiatric diseases as mental disorders, additionally supported the separation between neurology and psychiatry.

The application of scientific principles in psychiatry has later been established by Griesinger, Kahlbaum, Kraepelin and Maudsely, who created a consistent nosology and who regarded psychiatric diseases as diseases of the brain. Nevertheless, correlations between the clinical appearance and the pathological–anatomical substrate still remained unsuccessful. Whereas in the field of neurology, such correlations showed rising success, since neurological diseases could be localized anatomically–morphologically in the brain implying that they were regarded as "structural" diseases. The failure of structural localization of psychiatric diseases, in contrast, resulted in their acceptance as "functional" diseases with the meaning "psychological" and thus mental origin as distinguished from "structural" describing the "organic" and thus neuronal origin [97]. This opposition of "structure versus function" and "localization versus non-localization" accounted for the separation of neurology and psychiatry in a decisive manner; the neurologist dealt with structural diseases of the brain, the psychiatrist focused on functional diseases of the mind. This lead to the development of neurology and psychiatry as independent disciplines in the Anglo-American region whereas in the German-speaking regions both disciplines have been kept together for a long time in the common discipline of "Nervenheilkunde".

Changes in the relationship between neurology and psychiatry

Different developments in the last decades question the comparison of neurology and psychiatry. These developments mounted from both the fields: neurology and psychiatry; in the following they are shortly described. By the discovery of variability of the brain's neuronal structures, i.e., the plasticity, and the introduction of new imaging techniques (MRI, PET; see below) neurology changed its appearance: Solely static-structural observations have been replaced by a dynamic–functional anatomy [63]. This "functional neuroanatomy" not only examines different static structures but tries to point out the connections between these structures, to show plasticity of connections and structures as well as the influence of function on structure [117]. The boundaries between anatomy and physiology melt away because of this "functional neuroanatomy", where the contrast of anatomical-static structure and physiological-dynamic function is dismantled and rather regarded as a relationship of mutual complementation: "The boundaries between anatomy and physiology, between form and function, break down at an ultrastructural level. Anatomy is not static. Pharmacotherapy may alter structure as well as function." [63]. The new imaging techniques on the one hand allow to image anatomic structures more exactly and more detailed. On the other hand they make it possible to draw a connection between functional changes and anatomic structure—they are a kind of "window for the brain function" [11]. These developments make it possible, to look at psychiatric diseases, too. The physiologic-functional examination, which is still

Table 2 Characterization and definition of neuropsychiatry

Neuropsychiatry	Biological psychiatry	"Behavioral neurology"	Cognitive neurology
Diseases with neurological and/or psychiatric phenomena	Psychiatric diseases	Neurological diseases	Neurological disorders with cognitive dysfunction
Functional and structural aspects as complementary	Functional	Structural	Functional and structural aspects
Dynamic–functional localization	Localization in functional micro structures	Localization in static anatomic macro structures	Localization in dynamic anatomic macrostructures
Clinical–functional–dynamic correlations	Clinical–neurochemical correlations	Clinical–pathological correlations	Clinical–anatomo–functional correlation
Functional brain	Neurochemical brain	Anatomical brain	Functional brain

getting off the ground, could shed new light on the pathophysiology of psychiatric diseases.

The development of psychopharmacology supported the hypothesis already set by Griesinger that mental diseases are diseases of the brain. The question of the mechanisms of the pharmacological effects in the brain by psychopharmacological drugs resulted in an intensive exploration of neurotransmitters, synapses and receptors in the brain, which itself resulted in a better and extended understanding of physiological brain functions. Out of this the discipline of "biological psychiatry" emerged, which tries to correlate psychopathological phenomena with functional and structural changes in the brain [118]. Initially "Biological psychiatry" mainly dealt with synapses, neurotransmitters and receptors; by examination of the mechanisms of effectiveness one tries to gain insight into the structural and functional events in the brain in psychiatric symptoms and diseases.

Not only in psychiatry changes have happened, but also in neurosciences and in neurology. Over the last 10–20 years, neuroscience shifted its interested more and more on affective and cognitive functions like working memory [57], emotional perception and judgment [32, 74, 88], attention [84, 85], and even originally philosophical notions like consciousness [44] and self [124]. This has lead to the development of novel disciplines like cognitive neuroscience and affective neuroscience [81] which, because of their interest in more complex affective and cognitive functions, focus on those neural processes that allow to integrate and coordinate neural activity across different regions implicating complex neural networks in predominantly functional terms. Such coordination and organization of neural activity may for instance be achieved by plastic changes allowing neural activity to adapt to the respective challenges and tasks required. Another such mechanism recently discussed is the synchronization of neural activity across different brain regions by coordination of their frequency as for instance by gamma-band oscillations that are currently discussed to be possibly crucial in constituting consciousness [44, 113]. Based on these developments, neurology showed a rising interest in complex phenomena and behavior which could not clearly be traced back to reflexes [10]. Here the insufficiency of classic neurology became clear [52]—because of this mainly in America the discipline of "behavioral neurology" developed. It deals with complex phenomena like aphasia and amnesia and tries to localize these phenomena neurologically and neuroanatomically, respectively [18]. The old method of clinical–pathological correlations (see above) is here applied in a new field of interest, the field of higher-order cognitive phenomena and complex behavior,—in doing so the focus is still on structure and the aim of localization [63]. This, however, is changing and the focus on "anatomic static macrostructures" becomes more and more complemented by considering "functional dynamic macrostructures" which in turn allows to account for higher-order cognitive phenomena like attention, theory of mind, etc. (see for instance Refs. [84, 85]). This is the focus of a recently developed special branch of neurology, *Cognitive Neurology*, which therefore may be regarded as paradigmatic subset of a neuropsychiatry in a current gestalt. *Cognitive Neurology* investigates cognitive dysfunctions for instance attention or theory of mind in neurological disorders like Parkinson's disorder and is therefore able to draw interesting parallels with psychiatric disorders like catatonia [69].

The discipline of "neuropsychology", constantly developing in the last years, too, examines the "correlations between brain function and psychological processes" [91] closely following classical neuropathology [41, 91]. The separation between neuropsychology on one hand and "behavioral neurology" on the other hand is mainly in the USA pursued. In "behavioral neurology" mainly aphasia and amnesia are investigated. The main topic of neuropsychology is to provide objective methods for the examination of psychological function, which then can be applied on the clinical problems as dealt with in "behavioral neurology" and set into relationship to brain structure and function [3]. The "behavioral neurologist" primarily looks at the structures of the brain and secondarily their relation to complex psychological functions. The neuropsychologist, on the contrary, regards primarily the psychological functions and secondarily their relation to the structures of the brain [18]. The neuropsychologist captures affective and cognitive alterations in the Parkinson's disease using standardized tests in an objective manner—the correlation of these results with structures und functions of the brain is left to the neurologist to a large extent. The quantitative, operationalized measurement of psychological functions, the so-called psychometrics [41], is increasingly used in psychiatry, too, where psychopathological phenomena are captured quantitatively and objectively by operationalization of the psychopathological symptoms. Thus the psychopathology which previously often has been called non-scientific becomes affiliated with an "empiric–scientific methodology" [64] thereby gaining scientific status.

The above described developments of different disciplines in the border area between neurology and psychiatry aim to bridge the contrasts between both fields from different directions (biological psychiatry, behavioral neurology, neuropsychology, and cognitive neurology) [63]. All these disciplines would explain the above described example of Parkinson's disease differently: The biological psychiatrist localizes the affective and cognitive symptoms in the microstructure of the transmitters, synapses and receptors; the "behavioral neurologist" localizes the same symptoms in the macro structures of the brain; the neuropsy-

chologist objectivizes and standardizes psychological functions; and the cognitive neurologist would point out the anatomo-functional networks of the cognitive symptoms. All of them (with probably the exception of the cognitive neurologist) place motor/neurological and psychiatric symptoms next to each other and explain them more or less independently from each other—the internal connection of motor and psychological alterations in the Parkinson's disease as experienced by the patient gets lost. Because of this in the following we want to show that a neuropsychiatry could be able to demonstrate these internal connections between psyche and motor activity.

Neuropsychiatry: characterization and definition

The discipline of neuropsychiatry tries to bridge the gap between neurology on the one hand and psychiatry on the other hand—in doing so psychological functions and neurological structures are not only to be observed in the same time but are to be connected internally coherently: "This new orientation of which Jellife spoke, and of which he himself was a notable exemplar, did not involve merely combining neurological and psychiatric knowledge (as every neurologist and psychiatrist does to some extent), but conjoining them seeing them as inseparable, seeing how psychiatric phenomena might emerge from the physiological, or how, conversely, they might be transformed into it—..." [63]. The static-structural, strictly localizing observation of the classic neurology and the "behavioral neurology" will be contrasted by a dynamic-functional approach of the neuropsychiatry. Psychological and motor alterations in the Parkinson's disease are no longer explained separately and independently but are regarded as two expressions of a uniform dynamic-functional structure—the alteration of this structure, and not of the two different symptom complexes as two different phenomena, have to be explained. Thus the "neurologilization" of psychiatric functions [63] is impossible—behavior can not only be observed with neurological methodology, but has to be assessed by integration of neurological and psychiatric knowledge [63].

Biological psychiatry can not be identified with and reduced to neuropsychology, because it does not exclusively deal with complex macro phenomena of behavior and psychological functions, but with micro phenomena of the synapses, transmitters and receptors—psychological functions mainly remain beyond observation [13]. While biological psychiatry uses functional neuroanatomy, restricting it to microstructures (synapses), behavioral neurology focuses on macrostructures of the brain though considering them solely in a static, anatomic-structural sense. Neuropsychiatry should aim to combine the dynamic-functional approach with the observation of macrostructures in the phenomena of behavior and higher-order psychological functions. In other terms, neuropsychiatry in this sense would take a middle position between a static-structural, localizing neurology on the one hand and a dynamic-functional, holistic/anti-localizing psychiatry on the other. As a bridge between neuroanatomy and psychopathology neuropsychiatry has to examine functional and dynamic processes being positioned in between strictly localizable neurological functions and strictly holistic psychological processes [79]. This middle level of neuropsychiatry undermines the traditional opposition of structure versus function and localization versus non-localization.

Function, localization and neuronal integration in neuropsychiatry

Function and localization

I already mentioned the contrast of structure versus function and characterized the latter as crucial for the discipline of neuropsychiatry. What does the term "function" mean? "Functional" can be understood in two senses [99]: Firstly, "functional" means just non-organic and thus psychological, as it has been understood in psychiatry. Secondly, "functional" can be understood in a physiological sense in contrast to anatomic—here "functional" describes dynamic, plastic and variable physiological processes, being in contrast to the static, anatomic structure; this second meaning of the word "functional" has been used in the characterization of functional neuroanatomy (see above). I here want to follow the second and original meaning of the word "functional" [118] and regard the physiologic-functional description as middle level between static-structural pathology and dynamic-functional psychiatry as the specific neuropsychiatric level [79] which is now more and more taken into account in empirical and explanatory regard in both current neurology and psychiatry when considering affective and cognitive dysfunction in their respective disorders [69, 109, 113, 120, 123, 126]. Physiologic functions may not correlate with a specific static anatomic structure any more, but they develop in so-called functional systems [51, 52]. These systems produce distinct functions by a dynamic constellation of changes between different parts of the brain reflecting what may be called neuronal integration (see below). As demonstrated by current investigations of neuroplasticity in both healthy and psychiatric subjects (see Ref. [125]), they are plastic, show a systemic (and not a concrete) structure, and operate by dynamic auto regulation [51]. The realization of function depends then on dynamic systems that include different brain regions which Luria characterized as "functional systems": "According to this view a function is, in fact, a functional system (...) directed towards the performance of a particular biological

task and consisted of a group of interconnected acts that produce the corresponding biological effect. The most significant feature of a functional system is that, as a rule, it is based on a complex dynamic "constellation" of connections, situated at different levels of the nervous system, that in the performance of the adaptive task, may be changed with the task itself may be unchanged." [51].

The brain here is regarded as a network consisting of different, overlapping functional systems with an internal dynamic, a so-called "neurodynamic" [63], which have already been demonstrated in the form of "resonant oscillator circuits" for the brain [108]. For our example of Parkinson's disease this would mean, that the functional interaction of the functional systems of motor action, affect/emotion and cognition and their "interfunctional relation" [121] are altered. The motor action cannot be observed separated from affect/emotion and cognition because of the mutually overlapping systems—between the different functional systems there are so-called "functional knots" [52], enabling the motor action to influence affect/emotion and cognition directly, and reverse. This is, for instance, a model of Parkinson's disorder that is currently pursued in Cognitive Neurology.

What does this neuropsychiatric network with its interconnections between the different functional systems imply for the problem of localization versus non-localization and consecutively for the separation between neurology and psychiatry? Historically and currently, the discussion of mental processes is often characterized by the opposition of localizationists, who claim for exact localizability of mental processes in structures of the brain, and holists or aquipotentionalists, who believed that all structures of the brain are necessary for mental processes [36]. Both approaches can be considered "psycho morphological attempts" [52] which give priority to either the structural–functional differentiation/specialization of the brain (localizationists) or to the plasticity of the brain (holists) as visible in functional restitution following structural lesions. A dynamic-functional neuropsychiatry regards both positions as different aspects of the organization of the neuronal network without either aspect prevailing or dominating. Neuropsychiatry aims to combine both positions in a concept of "systemic–dynamic localization." [52] In this concept a function cannot be localized in a distinct anatomic structure but in a functional system with its functional interconnections. On the other hand no anatomic structure of the brain can be assigned to only one function, but it is always involved in different functional systems simultaneously or successively—Luria calls this "functional pluripotentialism." [52]

This "functional pluripotentialism" the functional overlaps, the "functional knots", of the functional systems of affection, cognition and motor action as well as their connection in the case of the Parkinson's disease. This can be localized neither in a distinct anatomic structure (localizationists) nor in the whole brain (holists)—a distinct kind of alteration of the functional interaction of the functional systems of motor action, affect/emotion and cognition is represented by the dynamic-functional localization in the Parkinson's disease. This makes clear, that traditional contrasts of structure versus function and localization versus non-localization, which resulted in the separation of neurology and psychiatry (see above), can no longer be maintained in the present form and could be bridged by a dynamic-functional neuropsychiatry. The middle level between structural localization and functional holism of mental states may be characterized dynamic-functional which may be realized by what can be called neuronal integration. This is well apparent in current psychiatry, particularly biological psychiatry, and cognitive neurology that both consider affective and cognitive dysfunctions in their respective disorders in such dynamic-functional terms thereby revealing different mechanisms of neuronal integration and their specific ways of alterations in these patients [69, 90, 92, 113, 120].

Neuronal integration

Neuronal integration describes the coordination and adjustment of neuronal activity across multiple brain regions. The interaction between distant and remote brain areas is considered necessary for a complex function to occur, such as emotion or cognition [21, 92]. Neuronal integration focusing on the interaction between two or more brain regions must be distinguished from neuronal segregation [21, 92]. Here a particular cognitive or emotional function or processing capacity is ascribed to neural activity in a single area that is both necessary and sufficient; one can subsequently speak of neuronal specialization and localization. We assume that higher psychological functions as complex emotional–cognitive interactions cannot be localized in specialized or segregated brain regions. Instead, we assume that higher psychological functions require interaction between different brain regions and thus neuronal integration as it is currently emphasized in both biological psychiatry and cognitive neurology in their focus on brain imaging of affective and cognitive dysfunction.

For neuronal integration to be possible, distant and remote brain regions have to be linked together which is provided by connectivity. Connectivity describes the relation between neural activity in different brain areas. There is anatomical connectivity for which we will use the term connections in order to clearly distinguish it from functional connectivity. In addition, Friston and Price [26] distinguish between functional and effective connectivity: Functional connectivity describes the "correlation between remote neurophysiological events" which might be due to either direct interaction between the events or other factors

mediating both events. A correlation can either indicate a direct influence of one brain area on another or their indirect linkage via other factors. In the first case the correlation is due to the interaction itself whereas in the second the correlation might be due to other rather indirect factors like for example stimuli based on common inputs. In contrast, effective connectivity describes the direct interaction between brain areas, it "refers explicitly to the (direct) influence that one neural system exerts over another, either at a synaptic or population level." [26] Here, effective connectivity is considered on the population level because this corresponds best to the level of different brain regions investigated here. For example, the prefrontal cortex might modulate its effective connectivity with subcortical regions thereby influencing specific functions like for example interoceptive processing. Based upon connectivity, neural activity between distant and remote brain regions has to be adjusted, coordinated, and harmonized. Coordination and adjustment of neural activity might not be arbitrarily but guided by certain principles of neuronal integration [72]. These principles describe functional mechanisms according to which the neural activity between remote and distant brain regions is organized and coordinated as for instance in top-down modulation (see also [68]). Another mechanism of how to integrate and coordinate neural across different brain regions is the synchronization of their frequency ranges as it has for instance been demonstrated in the case of gamma-band oscillations that are supposed to allow for those complex integrational processes that may underlie consciousness [44, 113].

Examples of neuronal integration

In the following, I briefly want to discuss some examples of neuronal integration that might be particularly relevant for neuropsychiatric disorders.

Top-down modulation and posttraumatic stress disorder

Top-down modulation might be described as modulation of hierarchically lower regions by those being higher in the hierarchy. Often top-down modulation concerns modulation of neural activity in subcortical regions by cortical regions. For example, premotor/motor cortical regions might modulate neural activity in subcortical basal ganglia like the caudate and striatum [54, 68]. Yet another example is top-down modulation of primary visual cortex by prefrontal cortical regions which has been shown to be essential in visual processing [44]. Top-down modulation might be related to the concepts of "re-entrant circuitry" [113] and feedback modulation [43]. These concepts allow for circuiting of information and readjustment of neural activity in one area according to another rather distant area. This provides the possibility of adjusting, filtering, and tuning neural activity in the lower area according to the one in the higher area. For example, top-down modulation allows for attentional modulation of visual input which makes selective visual perception possible [43].

I here want to focus on the medial prefrontal cortex. Neural activity in both medial prefrontal cortex and amygdala has been shown to be involved in emotional processing [65, 87]. Their functional relationship is supposed to be characterized by top-down modulation of the amygdala by the medial prefrontal cortex [14, 84, 85, 104]. Medial prefrontal cortical regions seem to exert also top-down control of neural activity in the insula [66] that is densely and reciprocally connected with subcortical medial regions like the hypothalamus, the periaquaeductal grey (PAG), the substantia nigra, and various brain stem nuclei such as the raphe nuclei and the locus coeruleus [81, 82].

Both the amygdala and the subcortical medial regions are involved in regulating internal bodily functions whereas medial prefrontal cortical regions have been associated with emotional processing [65, 71, 87]. The three regions, medial prefrontal cortex, amygdala, and subcortical medial regions, show dense and reciprocal connections [80–82]. Therefore one might assume modulation between all of them. This might not only include top-down modulation, as illustrated, but also the reverse kind of modulation, bottom-up modulation (see Fig. 1). In the case of bottom-up modulation a hierarchically lower area modulates activity in an area being higher in the hierarchy. For example, subcortical midline regions might modulate neural activity in medial prefrontal cortex via the insula thus concerning the same regions as top-down modulation. Accordingly, bottom-up and top-down modulation might co-occur across the same regions (see Fig. 1).

Functionally, this co-occurrence of bottom-up and top-down modulation might allow for reciprocal adjustment between emotional and internal bodily processing. Internal bodily processing concerns only stimuli from the own body, so-called internal self-related stimuli. These include for example stimuli from autonomic-vegetative or other humoral functions. Whereas emotional processing concerns both internal self-related and thus internal bodily stimuli and external self-related stimuli from the environment. For example, emotional processing might be induced by specific events within the environment which in turn might induce internal bodily stimuli. Since however neither studies about the functional relationship between the three regions nor between both kinds of processing have been reported yet, our assumptions must be considered preliminary and speculative. Psychologically, the co-occurrence of top-down and bottom-up modulation might correspond to the co-occurrence between emotional and bodily

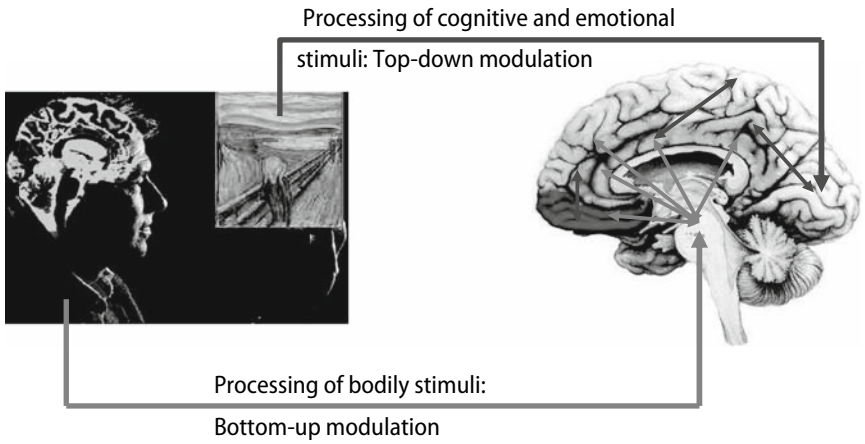

Fig. 1 Schematic illustration of bottom-up and top-down modulation between subcortical and cortical networks

awareness. We are aware of the emotions associated with certain events in the environment. This co-occurs with awareness of one's own body which usually remains in the background. Such co-occurrence Such co-occurrence might account for our predominant outward focus, directing our attention towards other persons and events in our environment whereas the inward focus, directing our attention towards our own body is not as central and predominant and seems to remain in the background.

Posttraumatic stress disorder (PTSD) can be characterized by a constellation of symptoms in the aftermath of a severe emotionally traumatic event. The cardinal triad of clinical features includes: re-experiencing phenomena, e.g., flashbacks, which can occur spontaneously or in response to reminders of the traumatic event; hyperarousal, e.g., exaggerated startle response; and avoidance, e.g., avoiding situations that remind the individual of the traumatic event (see Ref. [96] for an overview). The symptoms in PTSD can thus be characterized by a combination of emotional and vegetative disturbances. Recent imaging studies observed abnormalities in the anterior cortical midline structures including the VMPFC and the supragenual anterior cingulate cortex (see Refs. [47, 96]. These regions have been associated with the inability of PTSD patients to extinct threatening stimuli and their inability to suppress attention to trauma-related stimuli. Since the very same regions are also involved in mediating self-related processing, Liberzon and Martis [47] assume that self-related processing may also be altered in PTSD which however remains to be shown. Another region that has been shown to be abnormal is the amygdala that shows exaggerated responses which may mediate the abnormal hyperarousal in PTSD patients [96]. Finally, the hippocampus has also been shown to be deficient in neural activity. One may consequently assume altered balance and thus top-down modulation between cortical and subcortical midline regions in PTSD (see Ref. [96]) during emotional and self-related processing. Studies investigating functional and effective connectivity indicate that cortical control and top down-modulation of subcortical neural activity in the amygdala may be altered in PTSD [47, 96] for which however further empirical support is needed. Altered cortical–subcortical balance may psychologically result in "exuberant acquisition of conditioned fear and exaggerated fear responses, as well as deficient extinction recall and an incapacity to appreciate safe contexts." [96]

Reciprocal modulation and depression

Recent studies [27, 28, 71, 72] demonstrate a pattern of opposite signal changes in medial and lateral prefrontal cortex during emotional–cognitive interaction. These results are compatible with the assumption of functional mechanisms of reciprocal modulation and reciprocal attenuation during emotional–cognitive interaction. Reciprocal modulation can be defined by signal changes in opposite directions (i.e., signal increases and decreases) in different regions. For example, emotional picture viewing is known to lead to signal increases in medial prefrontal cortical regions and concurrent signal decreases in lateral prefrontal cortex [65, 72, 87]. In contrast, cognitive tasks like judgment or evaluation induce the reverse pattern with signal increases in lateral prefrontal cortex and signal decreases in medial prefrontal cortex. This is compatible with the functional mechanism of reciprocal modulation (see Fig. 2 and Ref. [72]). Interestingly, analogous patterns of reciprocal modulation have been observed in other cortical regions including

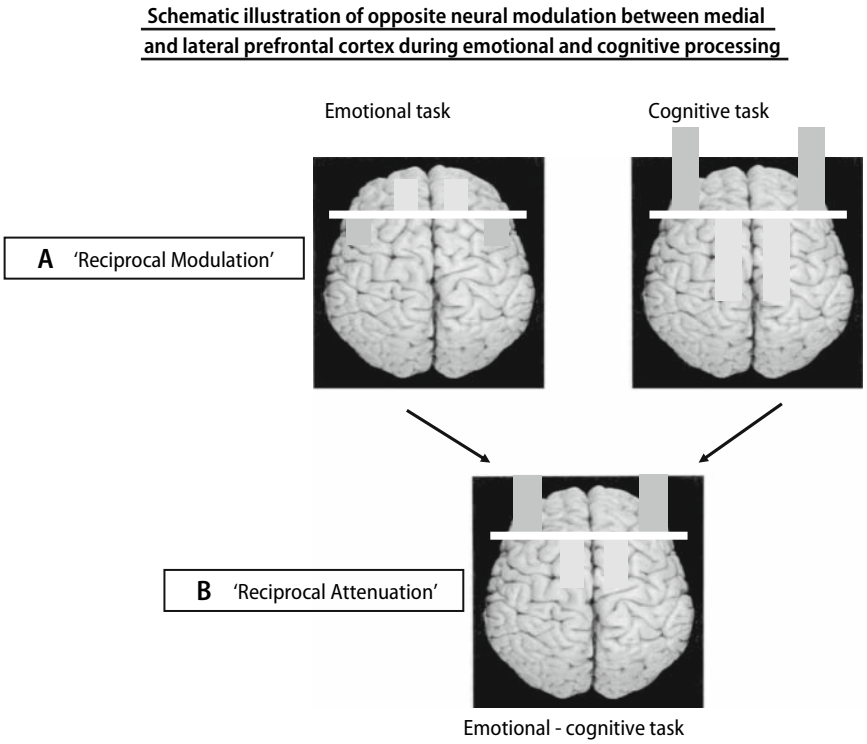

Fig. 2 Schematic illustration of opposite neural modulation between medial and lateral prefrontal cortex during emotional and cognitive processing

medial and lateral orbitofrontal cortex [71–74, 77, 78] right and left motor cortex [1], striate and extrastriate visual cortex [40], subgenual anterior cingulate and right prefrontal cortex [48], sub/pre- and supragenual anterior cingulate [9] as well as visual and auditory cortex [45, 46]. Emotional–cognitive interaction is then associated with the functional mechanism of reciprocal attenuation: Inclusion of an emotional component into a cognitive task resulting in for example emotional judgment leads to smaller signal decreases in medial prefrontal cortical regions and, at the same time, smaller signal increases in lateral prefrontal cortical regions; this has been called attenuation [72]. Since attenuation concerned both medial and lateral prefrontal cortical regions in opposite directions (i.e., smaller signal decreases/increases, respectively), one can speak of reciprocal attenuation.

Depression, e.g., major depressive disorder (MDD), can be characterized by co-occurrence of affective and cognitive symptoms. Affectively depressed patients can be characterized by the inability to experience and obtain pleasure, e.g., anhedonia, resulting an abnormal sadness. Cognitively, depressed patients are no longer able to evaluate their own emotional and bodily experience appropriately; the judgments of their own states are "subjectively" distorted and decoupled from "objective" reality. Subjective distortion is manifest in the extreme negativity of their judgments concerning either their own emotions and their own body or emotions in other persons and events in their environment. This extreme negativity corresponds to what psychologically has been described as the "negative bias" [16, 29]. Functional imaging studies in depression [55, 56, 88] show hyperactivity in medial prefrontal cortex and hypoactivity in lateral prefrontal cortex during emotional stimulation [16, 48, 55, 56]. This corresponds indeed to abnormal reciprocal modulation between medial and lateral prefrontal cortex. What however remains to be shown is that this abnormal neural activity in medial and lateral prefrontal cortex is related to emotional and cognitive dysfunction (see Ref. [32]). Furthermore, abnormal reciprocal attenuation during emotional–cognitive interaction has not been demonstrated yet in depressed patients.

Modulation by reversal and phobia

Several studies demonstrated reversal of signal changes in the opposite direction within the same region. Signal changes within the OMPFC, were, for example, reversed (from signal increases to signal decreases) by either preceding (like expectancy) or simultaneous (like distraction or increased focus) attentional manipulation of emotional stimulation. To account for attentional modulation in the paradigm, emotional pictures were either preceded by an expectancy period or by a simultaneous flickering [38, 90, 95, 106, 107]. A recent study [73] observed reversion of signal increases to signal decreases in both OMPFC and posterior cingulate cortex when emotional judgment was preceded by an expectancy period. Similar changes in signal direction were also observed in cognitive tasks during attentional modulation. For example, noun generation, object

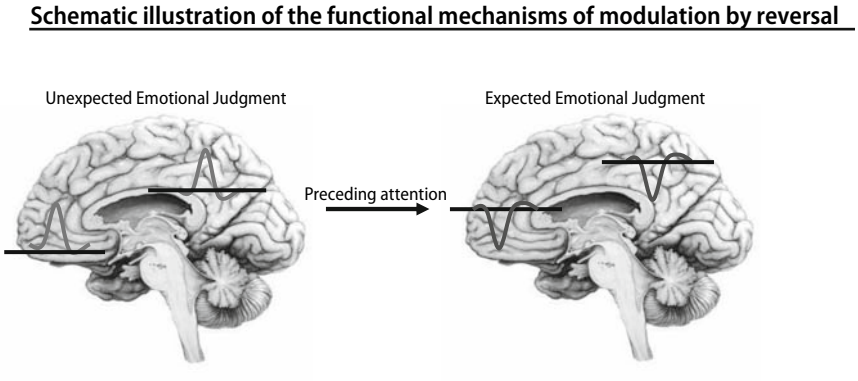

Fig. 3 Schematic illustration of the functional mechanisms of modulation by reversal

knowledge, and impersonal/personal word judgment tasks [17, 39, 59, 106, 107] induced similar signal decreases in OMPFC. "In other words, neural activity in response to an emotional stimulus is dependent on whether the stimulus was expected or not; expected stimuli results signal increases and unexpected stimuli results in decreases."

Analogous signal changes in OMPFC have also been observed in reward studies in both humans and monkeys. Expectancy of reward delivery induces signal increases (in humans) and neuronal excitation (in monkeys) in the OMPFC during the expectancy period itself. If, however, the reward delivery is delayed, omitted, or devalued, signal decreases (in humans) and neuronal inhibition (in monkeys) can be observed in OMPFC [2, 6, 30, 42, 58, 62, 75, 100–103, 112, 114, 115]. Moreover, modulation by reversal has also been observed in OMPFC during switch from abstract reward to punishment. The OMPFC showed true signal increases during reward which were reversed into signal decreases during punishment [12, 75–78]. Taken together, these findings are well compatible with the functional mechanism of modulation by reversal: A modulating factor (i.e., expectancy) reverses the type of neural activity within a specific region (i.e., OMPFC) during a particular task (i.e., emotional judgment). The functional mechanism of modulation by reversal is schematically illustrated in Fig. 3.

Physiologically, the exact nature of signal decreases in fMRI, as distinguished from signal increases reflecting neuronal excitation, has not yet been elucidated [34, 49]. However, a recent study strongly suggests that signal decreases are largely a result of active neuronal inhibition [108]. If signal decreases indeed reflect neuronal inhibition and signal increases neuronal excitation, attentional manipulation reverses the type of predominant neural activity in a specific region during an emotional or cognitive task. The transformation of signal increases into signal decreases would then correspond to reversal of neuronal excitation into neuronal inhibition; the latter predominating the former. Functionally, such reversal in signal (or neuronal activity) type is supposed to reflect a new linkage between an externally-induced stimulus and an internally-generated behavioural response, i.e., stimulus–response associations (and consequently response–reward associations) [67]. Psychologically, the neuronal mechanism of modulation by reversal in OMPFC might account for the suppression of either reward- or emotional stimuli. If reward is modulated by either delay or punishing stimuli, signal changes in OMPFC are apparently reversed. Since delayed or punishing stimuli change the level of attention, these results suggest that signal decreases in OMPFC might be associated with attentional modulation. This indicates that signal changes during a specific emotional or cognitive task might also depend on the respective psychological context as, at least partially, reflected in preceding or simultaneous attention.

Phobia is psychologically characterized by strong and abnormal attention to that particular content/stimuli in relation to a particular emotional reaction. There is heightened preceding attention, i.e., expectancy which reaches abnormally high levels. Thoughts merely indicating the particular stimulus without its actual appearance can already be sufficient to elicit emotional reaction. Simultaneous attention might also be abnormally increased in these patients who remain unable to shift their emotional attention. We therefore predict that displacement in phobic patients is characterized by attentional alterations concerning preceding attention, i.e., expectancy, simultaneous attention, and selective and shifting attention. This is supported by recent studies showing increased selective attention to the respective stimuli in phobic patients [5, 86, 98]. Physiologically, the orbitomedial prefrontal cortex (OMPFC) seems to play a crucial role in attentional modulation. Therefore, we suggest that cognitive induction of signal decreases in OMPFC might be altered in phobic patients. This leads us to predict that phobic patients remain unable to reverse neural activity in OMPFC from signal increases to signal decreases during attentional modulation. Preceding expectancy might no longer induce signal reversal in OMPFC from signal increases to decreases. Instead, there might be increased signal increases in OMPFC which might remain immune to attentional modulation. This is indeed supported by recent

imaging studies with phobic patients showing stronger signal increases in medial cortical regions like the OMPFC and the anterior cingulate cortex as well as in closely connected regions like the amygdala and the insula during exposure to the respective stimuli [15, 50, 89, 110, 111, 119]. However, abnormal attentional modulation of neural activity in these regions by the different forms of attention remains to be shown.

Modulation by functional unity

Another example of a possible functional mechanism of emotional–cognitive interaction is the constitution of functional unities. Functional unity can be described the coordination of the neural activity over a limited time period by means of which different regions are linked together with respect to a particular function. Such transient functional unities might be identified based upon the psychophysiological characteristics or the functional connectivity of the respective regions [20–25]. The medial regions in our brain's cortex, the so-called cortical midline structures (CMS) can be considered a functional unity [71] which is supported by different lines of evidences. First, one can often observe co-involvement and co-activation of different midline regions. For example, the above describe mechanisms of modulation by reversal cannot only be observed in the OMPFC but also in posterior cingulate [73]. Other studies on emotions and cognitions show similar co-involvement of anterior and posterior midline regions [37, 71, 72]. Second, unlike other more lateral cortical regions and subcortical regions, the CMS show a continuous high level of neural activity during resting conditions such as passive viewing of a fixation of a cross [33, 34, 57, 93, 94]. Third, regions in the CMS are characterized by close anatomical connections and tight functional connectivity. For example, Greicius et al. [31] investigated the functional connectivity among CMS regions in both resting and activation state. They observed increased functional connectivity between anterior and posterior CMS regions in the resting state whereas it was decreased during active cognitive tasks. Taken together these findings are compatible with the functional mechanisms of modulation by functional unity. The described data provide compelling evidence for the existence of CMS as functional unity which seems to be particularly active and cohesive in the resting state [31, 122–124].

Catatonia is a psychomotor syndrome showing a unique constellation of affective, behavioral and motor symptoms [7, 8, 19, 68, 69]. Most impressively, acute catatonic patients are totally immobilized, posturing in bizarre positions, and becoming totally mute which may be associated with an uncontrollable overflow of anxieties, i.e., "immobilization by anxieties" [68, 69, 83]. Imaging studies during emotional stimulation showed altered pattern of signal changes in medial and lateral orbitofrontal cortex (MOFC and LOFC) in catatonic patients compared to non-catatonic psychiatric and healthy controls. Specifically, we observed reduced signal changes in the MOFC and enhanced signal changes in the LOFC during negative stimulus presentation (see Refs. [69, 72] for details). Correlation analysis of functional connectivity between OFC, MPFC, and premotor and motor cortex in catatonic patients as compared to non-catatonic psychiatric and healthy controls revealed the following differences: Catatonic patients showed significantly lower scores for functional connectivity from the orbitofrontal cortex to the medial prefrontal and the premotor/motor cortex when compared to non-catatonic psychiatric controls and healthy subjects. These findings of abnormal connectivity from orbitofrontal cortex over medial prefrontal cortex to premotor/motor cortex suggest abnormal modulation by functional unity in these patients. The functional unity across anterior cortical midline structures seems to be less coherent than in healthy subjects. This less coherent functional unity might in turn facilitate abnormal transformation of emotional symptoms into motor symptoms. Interestingly, patients with conversion symptoms that show a more or less analogous combination of emotional and motor symptoms seems to show similar neural abnormalities. Imaging studies in acute paralytic patients revealed deficits in various regions of the anterior CMS including the orbitofrontal and the premotor/motor cortex [35, 53, 109, 120]. Why however is there a symptomatic difference n between hysterical and catatonic patients the former showing conversion and the latter catatonia? It should first be noted that hysterical patients can show a catatonic-like picture and that, conversely, catatonic patients can appear strongly hysterical [60, 61, 68–70]. Such symptomatic overlap suggests that both catatonia and hysteria overlap in the neuronal mechanisms. They might share the abnormal functional unity of anterior CMS resulting in abnormal motor behavior. However, modulation by functional unity might not only concern overlapping regions but also different regions; this in turn might explain the symptomatic differences between catatonia and hysterical conversion. Future studies specifically targeting single catatonic or hysterical symptoms might reveal those neuronal mechanisms specifically associated with hysterical conversion as distinguished from those related to catatonia.

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